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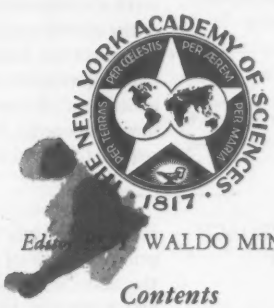
SER. II, VOL. 14 *May, 1952* NO. 7

TRANSACTIONS
OF
THE NEW YORK ACADEMY OF SCIENCES



Edi WALDO MINER

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TRANSACTIONS of The New York Academy of Sciences, Series II, Volume 14, No. 7, May, 1952.

Entered as second-class matter December 12, 1947, at the post office at Baltimore, Maryland, under the act of August 24, 1912. This publication is distributed to members and is published monthly from November to June, inclusive, by The New York Academy of Sciences, Mt. Royal and Guilford Aves., Baltimore 2, Md. Editorial office: 2 East Sixty-third Street, New York 21, New York.

Executive Director: EUNICE THOMAS MINER

THE FRACTIONATION OF THE SERUM PROTEIN BY ELECTROPHORESIS-CONVECTION*

By JOHN G. KIRKWOOD†

The electrophoresis-convection apparatus, developed by J. R. Cann, R. A. Brown, and the speaker, is based upon the same principles as those of the Clusius column, with the difference that horizontal electrophoretic transport, instead of transport by thermal diffusion, is superimposed on counter-current convective circulation in a vertical channel. Two reservoirs, connected by the vertical convection channel, contain a solution of the protein to be fractionated. Upon application of a horizontal electric field, differential transport of the mobile components across the channel takes place, producing a horizontal density gradient dependent upon the composition gradient. Under the action of gravity, the density gradient induces convective circulation in the channel with a velocity distribution qualitatively similar to that of the Clusius column. The result of super-position of the horizontal electrophoretic transport and vertical counter-current circulation is movement of the mobile components from the top reservoir to the bottom reservoir at rates dependent upon their electrophoretic mobilities, with a relative enrichment of the top reservoir with respect to slow components, and of the bottom reservoir with respect to fast components.

* This paper, illustrated with lantern slides, was presented at the meeting of the Section of Physics and Chemistry on March 4, 1952.

† Department of Chemistry, Yale University, New Haven, Connecticut.

THE PHYSICAL-CHEMICAL APPROACH TO THE PROBLEMS OF CHEMOTHERAPY*

By ALEXANDER V. TOLSTOOUHOV†

From the previous studies by the author and other investigators, it became evident that it was very often difficult and sometimes simply impossible) to find a correlation between the structure of compounds and their biological activity. This difficulty was especially pronounced with structurally complicated compounds such as antimalarials, local anesthetics, antiseptics, antiluetics, *etc.*

Entirely different relations are found when the biological activity is correlated with some physical-chemical characteristic of compounds, such as the dissociation constants or the reduction and oxidation potentials.

To illustrate this, we shall make the attempt to correlate the basicity of antihistaminics with their biological activity.

In the case of clinically useful compounds, the activity was derived from the various reports in current literature. Naturally, we cannot expect the desirable accuracy with such a kind of evaluation of biological activity. Nevertheless, it seems that it was possible to state that the most basic amines with pk_{hb} 9.13–9.07 or pk_b 5.01 5.09 are generally the least toxic, and that they still possess the desirable clinical effects. Those most toxic, and producing the longer-lasting effect, are the amines with pK_{hb} 7.56 and 7.44 or pK_b 6.50–6.58.

In the case of diamines, their basicity, expressed by their dissociation constants, was compared with the percentage of inhibition of histamine contraction of guinea pig ileum. The biological testing was done by Miss Christine Russo in our laboratories.

The dissociation constants of antihistaminics were calculated from the hydrolysis of their hydrochlorides according to the method of H. G. Denham.[1] The following terms were used in the text:

$BOH \rightleftharpoons B^+ + OH^-$, or, from the law of mass action:

$$K_b = \frac{(B^+)\cdot(OH^-)}{(BOH)} \qquad (1)$$

$pK_b = -\log K_b$.

In the case of the salt of a weak base and a strong acid dissolved in water:

$BCl + H_2O \rightleftharpoons BOH + H^+ + Cl^-$ or, from the law of mass action:

$$K_{hb} = \frac{(BOH)\cdot(H^+)}{(B^+)} \qquad (2)$$

* This paper, illustrated with lantern slides, was presented at a meeting of the Section of Physics and Chemistry on April 1, 1952.

† Nepera Chemical Company, Yonkers, N. Y.

$pK_{hb} = -\log K_{hb}$. K_b is the dissociation constant of a base. K_{hb} is the hydrolytic constant of a base or, according to some authors, the dissociation constant of an acid. Personally, we prefer the original term introduced by H. G. Denham[1] as a less confusing one.

From equations 1 and 2 we have:

$$K_b \cdot K_{hb} = \frac{(\overline{R}^+) \cdot (OH^-) \cdot (\overline{BOH}) \cdot (H^+)}{(\overline{BOH}) \cdot (\overline{R}^+)} = K_w \qquad (3)$$

or $pK_b = pK_w - pK_{hb}$, where K_w is the dissociation constant of water. The brackets indicate the activity, or, in dilute solutions, the concentration in mols per liter. (For the details of pH determinations and the calculations of the dissociation constants, see bibliographical reference 11.)

TABLE 1

THE LACK OF DIRECT PROPORTIONALITY OF INHIBITION OF HISTAMINE CONTRACTION OF GUINEA PIG ILEUM WITH DILUTION OF COMPOUND

pK_b'	*Percentage of inhibition* Drug dilution*	
	1/100,000	1/200,000
5.55	100	27
5.59	90	70
5.63	100	58
6.16	100	68
6.25	100	43
6.73	82	27

* Percentage of inhibition of histamine contraction of guinea pig ileum. (Refer to Reinhard's publication of the method here.)

The Diamines, Their pK_b and Biological Activity

It was found, in other instances, that the lowering of biological activity with the dilution of a drug is not in direct proportion to the dilution. The same was found in the present case of diamines (TABLE 1).

From this, it is evident that it is necessary to compare the activity of compounds at the highest dilutions. Only under these conditions is it possible to show the drop in activity of the most active compounds with increase of pK_b' above a certain level, namely from pK_b' of 5.59 to pK_b' of 6.46.

From TABLES 2–4, the following conclusions are evident:

1. Compounds with the best biological activity (antihistamine) have a pK_b' of 5.79 ± 0.24. Their activity (measured as a percentage of inhibition of histamine contraction of guinea pig ileum) is 58–70 per cent in dilution of the drug of 1/200,000.

2. Under similar conditions, the compounds with pK_b' lower (average pK_b' of 5.24 ± 0.24) or higher (average pK_b' of 6.46 ± 0.16) than this

TABLE 2

THE ANTIHISTAMINIC ACTIVITY OF THE MOST BASIC DIAMINES OF THE GENERAL FORMULA

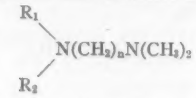
WHERE n, IF NOT INDICATED, EQUALS 2*

Percentage of inhibition†	pK_b'	R_1 / R_2
(1) 0	4.09	C_6H_{13}, CH_3; $N(CH_2)_3N(CH_3)_2$
(2) 0	4.09	C_6H_{11}, CH_3
(3) 0	4.48	C_6H_{13}, C_2H_5
(4) 0	4.54	C_6H_{11}, C_2H_5
(5) 0	4.69	C_4H_9, C_2H_5
(6) 0	4.77	$(C_3H_7)_2$
(7) 0	4.78	C_6H_{11}, CH_3
(8) 0	4.83	C_4H_9, CH_3
(9) 0	4.95	$(C_2H_5)_2$
(10) 0	5.25	$CH_2{=}CH{-}CH_2$, CH_3

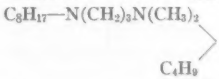
* Dilution of diamine: 1/50,000.
† Percentage of inhibition of histamine contraction of guinea pig ileum.

TABLE 3

THE ANTIHISTAMINIC ACTIVITY OF THE ACTIVE DIAMINES OF THE GENERAL FORMULA:



WHERE n, IF NOT INDICATED, EQUALS 2*

Percentage of inhibition†	$pK_{b'}$	
37	5.03	
33	5.29	
47	5.48	
27	5.55	
70	5.59	
58	5.63	
68	6.16	
43	6.26	
23	6.35	
40	6.50	
27	6.73	

* Histamine: 1×10^{-6}; compounds dilution: 1/200,000.

† Percentage of inhibition of histamine contraction of guinea pig ileum.

optimum $pK_{b'}$ possess the activity by only 32–33 per cent.

3. The biological (antihistamine) activity of the stronger bases (average $pK_{b'}$ 464) is nil.

From TABLE 5, the following conclusions can be drawn: (1) the basicity range of these amines varies between pK_{bb} 9.30 or $pK_{b'}$ 4.73 and pK_{bb} 7.44 or $pK_{b'}$ 6.58; (2) the necessary basicity can be accomplished either by the dialkyl amino group or by the imidazoline group (antistine); (3) the presence of the second basic group is unnecessary; and (4) it is evident that the variety of the rings can give the desirable clinical results.

The Reaction between Methylene Blue and Eosinic Acid at Various pH

Technique. Transfer into a series of test tubes, 2.5 cc of m/100 aqueous solutions of methylene blue and sodium eosinate, and varying amounts of N/10 NaOH and HCl and water to the total volume of ten cc. Mix, centrifuge, and measure the pH. Unlike the statements of previous workers in this field,[2, 3, 4] especially L. Pelet-Jolivet (1910)[5] the effect of the pH is striking.

TABLE 4

THE ANTIHISTAMINIC ACTIVITY OF THE SAME COMPOUNDS OF TABLE 3 DIVIDED INTO THREE GROUPS ACCORDING TO THEIR ACTIVITY

% of Inhibition 1 (see Table 1)	*Average* $pK_{b'}$
24–47% av. 32%	average $pK_{b'}$ 5.24 ± 0.20
58–70% av. 65%	average $pK_{b'}$ 5.79 ± 0.24
27–43% av. 33%	average $pK_{b'}$ 6.46 ± 0.16

Only the tubes with pH of 4.24 to 4.60 have the colorless supernatant fluid. Below pH 4.24, the supernatant fluid gradually becomes more and more intensely blue or purple blue. From pH of 4.60 up, the supernatant fluid becomes increasingly pink, and above pH of 5.42, purple.

This extreme sensitiveness of the above reaction to pH of the surrounding media can be explained as follows: (1) One of the two dyes, *i.e.*, methylene blue, is a comparatively strong base with $pK_{b'}$ of 2.77. The other dye, eosinic acid, contains two comparatively weak acid groups: —OH and —COOH, with $pK_{a'}$ of 3.86 and pK_{a_2} of 4.70. Therefore, eosinic acid can react in a different way at varying pH. At pH of 2.70 and lower, eosinic acid is practically undissociated and is completely

TABLE 5

THE CLINICALLY USED ANTIHISTAMINICS

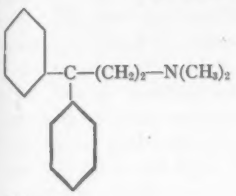
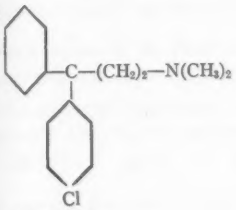
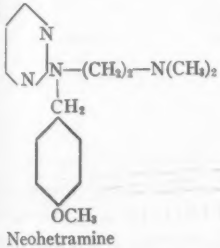
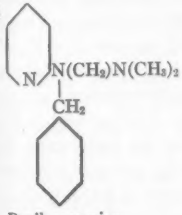
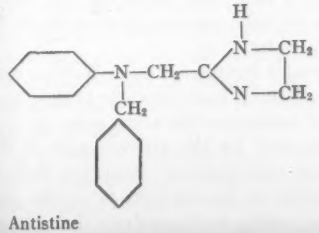
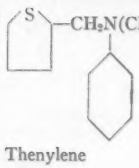
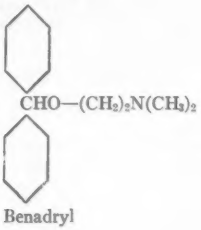
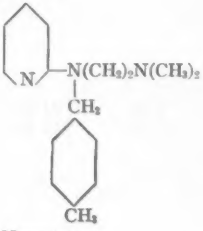
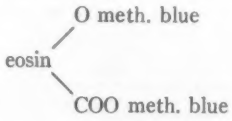
No. Antihistaminic	$pK_{Ab'}$	$pK_{b'}$	pK_{Ab_2}	pK_{b_2}
1  Trimeton	9.30	4.73		
2  Chlortrimeton	9.13	5.01		
3  Neohetramine	9.07 9.07	5.09 4.99	2.29 2.25	11.87 11.80
4  Pyribenzamine	8.70	5.29	4.19	9.80
5  Antistine	8.26	5.62		

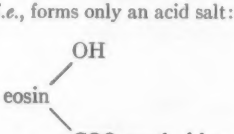
TABLE 5—*Continued*

No. Antihistaminic	pK_{b_1}'	pK_{b_2}'	pK_{bb_2}	pK_{b_2}
6  Thenylene	7.64	6.27	3.59	10.33
7  Benadryl	7.56	6.50		
8  Neoantergan	7.44	6.58	3.55	10.47

precipitated. At a pH slightly below 4.70 and higher, the eosinic acid begins to dissociate as a dibasic acid, *i.e.*, begins to form neutral salt:



Below pH 4.70, eosinic acid behaves as a monobasic acid, *i.e.*, forms only an acid salt:



As in the case of any other weak electrolytes, the percentage of dissociation varies gradually with a gradual change in pH of its solutions. This explains the gradual changes of color of supernatant fluid with changes in pH. From this gradual change of color of supernatant fluid, we learn about distributions of various ions among themselves. For example, from pH 4.80 to pH 5.30, the supernatant fluid gradually becomes more and more pink. This depends on a gradually increasing amount of neutral salt formed at higher and higher pH in comparison with the amount of acid salt. The acid salt was exclusively present between pH 4.24 and 4.60. Similar distributions are met within the selective staining of tissues and in drug action. From these studies, we understand also why pH is so important for the action of enzymes.[6]

To emphasize the importance of solvent, we can add that these reactions are absent in alcoholic solutions. To stain the tissues or the blood smears, the alcoholic solutions of dyes should be diluted with water.

Precipitation of Proteins by Dyes. Working with pulverized gelatin, J. Loeb[7] was able to show that a variety of substances like acids, salts, or even dyes can be used for the determination of the isoelectric points of proteins. Replacing the pulverized gelatine by the solutions of various proteins, it was possible to demonstrate that various

common biological dyes, such as methylene blue, safranine, acid fuchsin, and eosinic and picric acids, not only stain them but also precipitate them. This fact of actual binding of proteins by the dyes, or drugs in general, is very important for the understanding of the action of dyes or drugs. Similar precipitations are taking place between the various tissue proteins and so-called fixing fluids, antiseptics, or alkaloids. It was found that these complexes, or salts, are so stable that they change the iso-electric points of proteins or tissues for long periods of time. For example, the heavy metals stay in the body for years.

Determination of the Iso-electric Points of Tissue Ampholytes by Means of Staining at Various pH

A solution of a single dye, or a mixture of basic and acid dyes, can be used for the determination of iso-electric points of tissue ampholytes. When a mixture of two dyes is employed, it is necessary to keep them in a certain ratio.

Procedure. Prepare the series of test tubes containing the dyes' solutions at various pH; measure pH of the solutions; cover the previously fixed blood, bacteria smears, or tissue slides with the dye solution for 3 to 5 minutes; do not wash (to prevent the change of pH); simply remove the excess of dye with filter paper. If the air is sufficiently dry, wait for a few minutes or otherwise dry in dessicator, and cover with Canadian balsam or cedar oil. The iso-electric point of a particular tissue or granule, *i.e.*, the interpolated value of the pH, at which the staining with the various acid and basic dyes is at the minimum or is simultaneous, is taken.

As a result of these studies, it became evident that the selectivity of staining simply depends on the difference of the iso-electric points of various tissues. For example, in case of blood smears, the usual picture, when RBC (red blood cells) are stained by eosinic acid and WBC (white blood cells) by methylene blue, merely shows that at the pH of the dye mixture used for the staining, RBC were charged positively and WBC were charged negatively. The same dye mixture, but at a pH above the isoelectric point of hemoglobin (pH_i 6.8), stained RBC by methylene blue. It was observed that the staining is strictly reversible, *i.e.*, the same smear or slide can be used repeatedly for the staining at different pH.

It became possible to stain any tissue from bacteria to *spirocheta pallida* with the same mixture of dyes, using it only at certain pH.

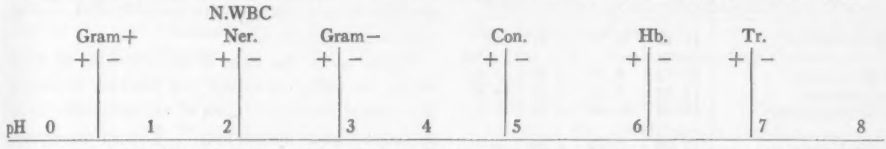
In TABLE 6 the great variations of the iso-electric points, *i.e.*, pH_i, of various tissues can be seen. For example, pH_i of *B. tuberculosis* is at a pH well below 1; gram positive and gram negative bacteria have different pH_i below pH 1 and between pH 2–3, consecutively; pH_i *spirocheta pallida* (*treponema pallida*) is at a pH near 7. The nearest to it is pH_i of hemoglobin, which is at a pH slightly above six (the accurate figure is 6.8); pH_i of the nervous system is at a pH slightly above two.

We realize that the values of pH_i just presented are only approximate because: (1) pH determinations of the dye solutions in our earlier experiments were made with hydrogen electrode; and (2) the iso-electric points of tissues fixed by various fixing fluids are not a true iso-electric point. In spite of that, it is evident that the iso-electric points of various microorganisms and tissues differ widely.

The knowledge of the pH_i permitted us to understand the selectivity of drug action. For example, it is evident that *treponema pallida* can be killed by negatively-charged drugs, such as Hg, Bi, organic arsenicals, penicillin, and terramycin. Here it can be seen that the structure of the drug is the least important.

TABLE 6

ISOELECTRIC POINTS* OF GRAM-POSITIVE AND GRAM-NEGATIVE BACTERIA, *TREPONEMA PALLIDA*, HEMOGLOBIN, CONNECTIVE TISSUE, NUCLEUS OF WHITE BLOOD CELLS (POLYMORPHONUCLEAR), NERVE CELL CYTOPLASM. BRAIN AND SPINAL CORD DETERMINED BY THE METHOD OF STAINING AT VARIOUS CONTROLLED pH†



* The vertical line indicates the isoelectric point. At lower pH, the ampholyte is positively charged, at higher pH, it is negative.
† Gram+ = gram positive microorganisms; N.WBC = nucleus of white blood cells (polymorphonuclear); Ner. = Nerve cell cytoplasm: brain or spinal cord; Gram− = gram-negative microorganism; Con. = connective tissues; Hb. = hemoglobin; and Tr. = *Treponema pallida.*

The proximity of pH_i of *treponema pallida* and hemoglobin explains why arsenic combines in the animal bodies almost exclusively with red blood cells.[28]

From the same table, it can be seen why the compounds acting on bacteria and nervous systems are positively charged bases, like alkaloids, local anesthetics, antihistaminics, sulpha drugs, and basic antibiotics.

Internal Antiseptics: Basic Azo Dyes

Two facts became evident after working with azo dyes having different basicity: (1) to kill gram negative bacteria, the dyes should be more basic than the dyes killing gram positive bacteria; and (2) a killing concentration of the same dye for gram negative bacteria is always much higher than the killing concentration of dye for gram positive bacteria.

TABLE 7
CORRELATION BETWEEN BIOLOGICAL ACTIVITY AND DISSOCIATION CONSTANTS AND ISOELECTRIC POINTS OF SOME SULPHA DRUGS

Name	pK_b	pK_a	pH_i	*Activity**
Metanilamide.....	11.11	10.16	6.47	0
Sulfapyridine.....	11.72	8.47	5.29	++
Sulfadiazine.....	11.84	7.17	4.62	++
p-Sulfanilamide.....	11.84	10.48	6.25	++
Sulfathiazole.....	12.09	7.49	4.69	++
Orthanilamide.....	12.80	10.22	5.67	0

* Activity on mice against *strept. hemolyticus*.

Carl L. Schmidt[12] has stated that two ampholytes with identical iso-electric points cannot react with each other, especially near their iso-electric points. In other words, ampholytes possess the smallest general toxicity and highest selectivity. From our own work with the dyes, we knew that strong basic dyes, like fuchsin, safranine, and gentian violet, with pK_b somewhere around 3.0 and 4.0, are more toxic than the the dyes like pyridium (pK_b 8.80), rhodamine (pK_b 9.43), and serenium (pK_b 11.44). All these considerations are fully supported by the experiments with sulfa drugs. Their general toxicity is very low.

From the proximity of the iso-electric points of bacteria and the nervous system, it was possible to predict the involvement of the nervous system, especially during the prolonged treatment with large doses of sulfa drugs. In the literature, toxic psychosis, neuritis, blindness, and convulsions[13] caused by sulfa drugs were reported.

Local Anesthetics

As was the case with antihistaminics, it was found that the biological activity depends on the proper pK_b,[14] or pH at which the free base of the anesthetic starts to separate.

The highest activity was shown by compounds with pK_b between 5.02 and 5.94, or by the compounds in which the free base starts to separate between pH 5.93 and 6.34. The compounds with the basicity outside of this optimum range showed gradually diminishing activity. Like previously-studied drugs, structurally the anesthetics can belong to various classes of compounds.

From the proximity of pK_b of antihistaminics and anesthetics, we can expect that both of them have the identical biological activity. This was proved experimentally with several compounds of these classes. As a matter of fact, procaine, especially in combination with ascorbic acid, can be used as an antihistaminic.[15, 16]

Again, as in the case of an overdose of sulfa drugs, we ought to expect the reaction involving the central nervous system of animals from these so-called "local anesthetics." The subcutaneous injections of local anesthetics, even in sub-lethal doses, invariably produced clonic epileptiform convulsions in animals. The same is taking place in human practice, where the similar convulsions can be produced sometimes after local application of the usual therapeutic dose of anesthetics. For the details, see C. A. Jackson.[17]

It is interesting to note that Maynard Murray and C. R. Hoffmann[18, 19] reported the presence of "guanidine like" substances in the blood of epileptics. The concentration of these substances increases at the time of onset of the seizures.

Neutralizations of Biological Effects of Drugs

The understanding that the selectivity of staining, or the drug's action, is a case of the redistribution of the base between several acids or *vice versa*, permitted us to apply the same approach to the problem of neutralizations of biological effects of basic drugs by acids, or *vice versa*. For example, if some drug[20] or toxin,[21] or even virus, acts on the nervous system, we can conclude that this activity depends on binding of the drug by the nervous system. To remove the drug from the nervous

system, it will be necessary to introduce into the animal body some other acid substance, capable of forming poorly dissociated salts or complex with it. The better examples of these simultaneous reactions are the precipitations of the mixture of the salts: $CrO_4 \cdot Cl$, CNS, I by silver.

Following these ideas, it became possible to neutralize the biological effects of nupercaine by the dyes of the type of trypan blue or by some sulphonated naphthalenes. More than that, it was possible to save the mice from strychnine poisoning by injecting into them the mixture of lethal dose of strychnine with pectin. In the case of strychnine, where the death follows the subcutaneous injection of it in two to three minutes, we cannot expect to save the animal by separate injections.

In the case of slower-acting nupercaine, it was possible to save the animal by injecting the abovementioned acid compounds immediately after nupercaine injection. Naturally, they should be given in the greatest possible excess for the best results (common ion effect).

S. S. Kety and T. V. Letonoff[22, 23] successfully treated the lead poisoning by intraveneous injections of sodium citrate. Very often, the effect was simply dramatic, especially in cases of severe colic, where even morphine could not stop the pains. S. S. Kety measured the dissociation constant of the salt (Pb citrate using lead electrode). The value of K_s is $10^{-5.74}$.

Fred R. Klenner[24] successfully used the large doses of ascorbic acid intravenously or intramuscularly for the treatment of polio, virus pneumonia, encephalitis, *etc.* The dose consisted of one to two grams of ascorbic acid every two hours.

Effect of Drugs on Cell Metabolism

From the data just presented, the drugs can act on the cell's metabolism in two ways: on their enzymes and the permeability of its membranes. It is generally recognized that all enzymes are proteins. The action of dyes or drugs consists of the formation of poorly soluble complexes or salts between them and tissue ampholytes, including enzymes. The solubility of these combinations are so poor that they produce a change of the iso-electric points of tissues for a long time (including enzymes). The tissues or enzymes with changed pH_i cannot react in the usual way. This will manifest itself in the changed metabolism of the cell. The effect of drugs on cell's membranes can be even more important, and the action of the drug will be very fast. In this case, the drug stays on the surface of the cell. Its action changes the semipermeability of the membrane only.

Especially from the works of Ralph Lillie,[25] and W. J. V. Osterhout,[26,27] we know already that the drugs can decrease or increase the permeability of the cell's membrane. The increase in the cell's membrane permeability is followed by the stimulation of the cell. The opposite takes place when the permeability is decreased. Incidentally, R. Lillie showed experimentally that the same drug (if at different concentrations) can reverse its activity.

Dissociation Constants of Salts

For more complete studies of the reactions between the bases and the acids, and especially for the studies of the distributions, it became necessary to calculate not only the dissociation constants of the bases and the acids, but also the dissociation constants of their salts, pK_s, or their counterpart hydrolytic dissociation constants, pK_{hs}.

The formulas for the calculations of the dissociation constants of the salts were calculated from pK_b and pK_a of the corresponding components of the salt.

From the pK_s of the salts, it became possible to calculate the percentages of the dissociation of the salt at any pH, and the concentration of the components.

It was found that many salts of the moderately strong bases and fatty, or aromatic, acids at pH *circa* 7 are dissociated only to the extent of 10 to 20 per cent, at the concentration of 1×10^{-2} or 1×10^{-3}.

By solving the simultaneous equations, it was possible to calculate the distribution of the base among several acids from their dissociation constants.

Conclusions

Convinced of the importance of the physical chemical characteristics of tissues and the drugs in chemotherapy, we propose to classify the compounds by their dissociation constants, or their iso-electric points. (Without that information, we are wasting our energy and money.)

For an illustration, we would remind you of what happened with antimalarials or antisyphilitics. Starting with two good compounds, quinine and atabrine, and preparing and testing at least 12,000 new compounds, we did not accomplish much.

Perhaps one or two of them could be found clinically useful. Still, we cannot explain why only these two compounds are good and why the others are bad.

The same thing happened with antisyphilitic or antitubercular compounds. Nobody was able to predict the antisyphilitic properties of penicillin.

All of this demonstrates that the structural chemistry is not sufficient to give the clear-cut correlations between the biological activity and the structure of the compounds.

Now, more than ever, we are convinced that only physical-chemical approaches to these problems can help solve them and provide us with the answers to these questions.

With the knowledge of these correlations, it will be easier to find the correlations between the structure and the physical-chemical characteristics of the compound.

The determinations of these constants are quite simple and can be carried out in any laboratory. The only necessary equipment is the modern pH meter with glass or, for the preliminary work with quinhydrone, electrodes.

Summary

(1) The action of the drug on tissues depends, like the staining, on the formation of undissociated, often very poorly soluble, complexes or salts between the tissues and the drug.

(2) Both the tissue's ampholytes and the drugs belong to the class of weak electrolytes. Because of that, the reactions between them are exceedingly sensitive to the pH of the surrounding media.

(3) The governing factors for these reactions of the drugs on tissues or microorganisms are their physical chemical characteristics, namely, dissociation constants, iso-electric points, pH of the media, and the solubilities of formed complexes or salts.

(4) It was observed that the compounds with identical biological properties and dissociation constants can belong to the different classes of compounds, possessing the different structures.

(5) Contrary to the previous statements, the compounds studied here always have diversified activities. For example, the antisyphilitic compounds can be bound by RBC (red blood cells), antihistaminics possess anesthetic properties.

(6) The solubilities of the salts or complexes formed between the drugs and the tissues, including the enzymes, are very often so poor that they can change their iso-electric points, *i.e.*, their normal activity, for a long time.

(7) If the reactions between the drugs and the tissues are taking place on the cell's membranes, they change the semipermeability of the cell's membranes and, by so doing, the functions of the cells.

(8) Instead of the usual classification, the compounds should be classified according to their physical-chemical characteristics.

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*SECTION OF BIOLOGY**

PHARMACOLOGY AND THERAPEUTIC VALUE OF DIAMIDINE DERIVATIVES —PARTICULARLY OF 2-HYDROXYSTILBAMIDINE†

By I. SNAPPER, B. SCHNEID, L. McVAY, AND F. LIEBEN‡ §

In 1939, stilbamidine and pentamidine were introduced for the treatment of kala azar.[1] These compounds proved to be effective even in patients who had been refractory to antimony treatment. Elson[2], in 1945, showed that these diamidines also inhibited the growth of *Blastomyces dermatitidis* and Schoenbach,[3] in 1951, treated two patients with North American blastomycosis successfully with stilbamidine. Unfortunately, the toxic effects of stilbamidine are so severe that it has been withdrawn from the market.

Two to three months after the stilbamidine treatment has been terminated, anesthesia to touch develops in one or all of the branches of the trigeminal nerve without loss of pain or heat sensation.[4–7] Subjectively, the patients complain of a "wooden" face usually associated with tingling and burning of the eyelids and forehead. Twitching of the face and eyelids occurs. These extremely disagreeable paresthesias do not develop immediately, but only a few months after the stilbamidine treatment is finished. They persist for months, sometimes even for years. The larger the total dose given, the more intense the trigeminal disturbance. There is no difficulty in detecting patients previously treated with stilbamidine by their expressions of misery, and blinking and tearful eyes. Whereas, in the dog, stilbamidine causes a diffuse degeneration of the gray matter of the brain,[8] in man it has a special affinity for the peripheral nervous system.

Stilbamidine causes this annoying side effect even in the relatively small doses (1.5 to 2.5 grams) which are necessary for the treatment of kala azar. Therefore, it can hardly be used for the treatment of maladies like blastomycosis and other fungus diseases where much larger quantities of stilbamidine are required in order to obtain a curative effect. In the course of the search for stilbamidine derivatives which would not cause the disabling trigeminal neuropathy, 2-hydroxystilbamidine was studied. It was known that this compound inhibits the growth of kala azar flagellates in the same concentrations as stilbamidine.[9] We first tried the 2-hydroxy compound, which had never before been used in humans, in the treatment of multiple myeloma and observed that this substance did not cause a trigeminal neuropathy.[10] We confirmed that the leishmanicidal action of 2-hydroxystilbamidine and of stilbamidine are nearly identical (TABLE 1). In addition, both compounds inhibit the growth of *Blastomyces dermatitidis* (TABLE 2) and of *Histoplasma capsulatum* in concentrations of a few micrograms per milliliter (TABLE 3). They also neutralize the action of cholinesterase, as was first described for stilbamidine by Nachmansohn.[11] The action of both diamidines on the mycelium phase of Blastomyces seems about equal, but stilbamidine may inhibit the growth of the yeast phase of Blastomyces, and of the mycelium and the yeast phases of Histoplasma, slightly better than 2-hydroxystilbamidine. There is considerable variation, however, in the outcome of such experiments.

Only five to ten per cent of the diamidines injected intravenously are excreted in the urine.[12] Far the greater part of the diamidines is deposited in various organs, especially in liver, kidneys, adrenals, and sweat glands, and remains there for many months, even years.[13]

By the use of the fluorescent microscope, stilbamidine can be found in the cytoplasm of the cells, combined with ribonucleic acid. However, 2-hydroxystilbamidine has a special affinity to desoxyribonucleic acid because, in microscopic sections of organs of individuals who have been in-

* A paper by Curt Teichert, entitled "An Australian View of Continental Drift," was presented at a meeting of the Section of Geology and Mineralogy on April 7, 1952. No abstract had been received at the time of publication.

† This paper was presented as the first of two papers in the Symposium on "The Diamidines in Pharmacology and Clinical Application" held by the Section of Biology on April 14, 1952.

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§ This investigation was supported in part by a grant of the U. S. Public Health Service.

jected with 2-hydroxystilbamidine, the nuclei are strongly fluorescent.[13, 14] When exposed to sunlight, a stilbamidine solution becomes toxic and less fluorescent, whereas the fluorescence of 2-hydroxystilbamidine hardly changes under influence of ultraviolet light. The inhibition of cholinesterase by irradiated stilbamidine or 2-hydroxystilbamidine decreases in direct proportion with the decrease of fluorescence. Therefore, irradiation decreases the anti-cholinesterase action of 2-hydroxystilbamidine much less than of stilbamidine (TABLE 4). Stilbamidine present in the nerves of the skin may well change under influence of sunlight to a toxic substance which causes the trigeminal neuropathy; whereas, in the case of the more stable 2-hydroxystilbamidine, no production of toxic substances results. This seems to be confirmed by the experience that, in this part of the world, the neuropathy is usually limited to the trigeminal area, whereas in the tropics, where arms and chest are usually bare, the neuropathy often involves also the trunk and the arms.

We have treated one case of South American leishmaniasis with 2-hydroxystilbamidine.[15] This patient was admitted in a deplorable condition with a weight loss of fifty pounds, a large nomatous gangrene of the left chest, and osteomyelitis of the underlying clavicle. There were only 850 leukocytes per cubic millimeter with 19 per cent polynuclear cells. The serum albumin was 3.4 grams per cent, and the globulin 4.3 grams per cent. Leishman Donovan bodies were found in the smears of the necrotic ulcer. A total dose of

TABLE 1

KALA AZAR FLAGELLATES, INOCULATED ON N.N.N. AGAR

	Growth
N.N.N.	+++
N.N.N. + 2 c.c. 2-OH Stilbamidine 1:20,000	−
N.N.N. + 1 c.c. 2-OH Stilbamidine 1:10,000 + 1 c.c. Arginine 1:40	−
N.N.N. + 2 c.c. Arginine 1:40	+++
N.N.N. + 2 c.c. Arginine 1:80	+++
N.N.N. + 2 c.c. Stilbamidine 1:10,000	−
N.N.N. + 1 c.c. Stilbamidine 1:5,000 + 1 c.c. Arginine 1:40	few
N.N.N. + 2 c.c. Arginine 1:40	+++

TABLE 2

COMPARISON OF INFLUENCE OF STILBAMIDINE AND OF 2-OH STILBAMIDINE ON *BLASTOMYCES DERMATITIDIS**

Concentration in mcrgr./cc.	*Mycelium (Saboureaud at 25%)*		*Yeast (Blood agar at 37%)*	
	Stilbamidine	*2-OH Stilbamidine*	*Stilbamidine*	*2-OH Stilbamidine*
Control	++	++	++	++
0.1	++	++	++	++
0.5	+	+	++	++
1	±	±	−	++
3	−	−	−	+
4	−	−	−	−

* Read after ten days.

TABLE 3

COMPARISON OF INFLUENCE OF STILBAMIDINE AND OF 2-OH STILBAMIDINE ON *HISTOPLASMA CAPSULATUM*

Concentration in mcrgr./c.c.	*Mycelium (Saboureaud at 25%)*		*Yeast (Blood agar at 37%)*	
	Stilbamidine	*2-OH Stilbamidine*	*Stilbamidine*	*2-OH Stilbamidine*
Control	++	++	++	++
3	++	++	++	++
5	+	++	−	++
7	±	++		
10	−	+	−	++
20	−	±	−	±
40	−	−	−	−

* Read after ten days.

TABLE 4

INFLUENCE OF ULTRAVIOLET RADIATION UPON FLUORESCENCE AND ANTI-CHOLINESTERASE ACTION OF STILBAMIDINE AND 2-OH STILBAMIDINE

	pH I	*pH II*	*Diff. in pH*	*Inhibition of cholinesterase*
1 c.c. hemolysate	7.62	6.44	1.18	
1 c.c. hemolysate	7.67	7.03	0.64	46%
1 c.c. hemolysate + 1 c.c. stilbamidine (irr.)	7.70	6.83	0.87	26%
1 c.c. hemolysate + 1 c.c. 2-OH stilbamidine	7.72	7.03	0.69	41%
1 c.c. hemolysate + 1 c.c. 2-OH stilbamidine (irr.)	7.72	6.95	0.77	35%

To each set 0.2 c.c. acetylcholine bromide (4.98 mg.) and 1 c.c. buffer are added.
pH I immediately, pH II 90′ after addition of acetylcholine.
Diamidine concentrations 10 mg. per cent.
After irradiation 54% of stilbamidine and 88% of 2-OH stilbamidine remained intact (fluorometric analysis).

6.1 grams of 2-hydroxystilbamidine, given in the course of four weeks, resulted in complete healing.

The first blastomycosis patient treated with 2-hydroxystilbamidine had been suffering from this disease since the spring of 1942. In 1951, the skin lesion had led to extreme disfigurement of the face. A miliary dissemination of blastomyces lesions through the lungs could be visualized on the roentgenograms. Blastomyces were found in cultures from skin biopsies, sputum and bronchial washings, and gastric washings. After a total of 12 grams of 2-hydroxystilbamidine had been given, all active skin lesions had disappeared with the exceptions of a small area on the forehead. The cultures of the gastric washings had become negative, and the X-ray picture of the lungs had cleared up completely.

The second patient with blastomycosis was 84 years old. He had a chronic granulomatous involvement of the upper lip and nasal area for about six years. Biopsy and culture of the skin lesions revealed *Blastomyces dermatitidis*. No fungi could be grown from gastric analysis and sputum examinations. After the patient had received a total of 2.8 grams of the 2-hydroxy compound, he was entirely asymptomatic. Only one lesion remained, measuring 0.8 by 1 cm. in the area of the right nasal labial fold.

In both cases, urinalysis, total blood count, blood urea nitrogen, and liver and kidney function, serum albumin and globulin, prothrombin time, and cephalin flocculation were determined regularly during the treatment and remained completely unchanged.

Summary

Stilbamidine, which had given very favorable results in the treatment of leishmaniasis and blastomycosis, had to be withdrawn from the market because it causes a toxic neuropathy, especially in the trigeminal area. It is shown that 2-hydroxystilbamidine inhibits the growth of leishmaniae, blastomyces, and histoplasma in test tube experiments in the same concentrations as stilbamidine, but it does not cause the trigeminal neuropathy. Both diamidines are deposited in the visceral organs and also in the skin. The action of stilbamidine is changed by ultraviolet light, much more than the action of 2-hydroxystilbamidine. It seems possible that stilbamidine, deposited in the skin, changes under influence of sunlight to toxic products which cause the trigeminal neuropathy. This may not happen in the case of the more stable 2-hydroxystilbamidine. Stilbamidine has more affinity to ribonucleic acid, and 2-hydroxystilbamidine to desoxyribonucleic acid. In microscopic sections of organs of individuals who have been injected with 2-hydroxystilbamidine, the nuclei are strongly fluoresecnt. One case of muco-cutaneous leishmaniasis and two cases of North American blastomycosis have been successfully treated with large amounts of 2-hydroxystilbamidine. No toxic neuropathy developed.

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THE USE OF THE AROMATIC DIAMIDINES FOR THE TREATMENT OF SYSTEMIC FUNGAL DISEASE*

By EMANUEL B. SCHOENBACH†

The studies of Warrington Yorke, J. D. Fulton, and their associates demonstrated the clinical usefulness of the aromatic diamidines in the treatment of trypanosomal and leishmanial infections. The compounds which have been investigated most extensively have been stilbamidine (4,4′-stilbenedicarboxamidine), propamidine [p,p′-(trimethylenedioxy) dibenzamidine], pentamidine [p,p′-(pentamethylenedioxy) dibenzamidine], and phenamidine (p,p′-xoydibenzamidine).[1]

In addition to their antitrypanosomal and leishmanial activity, the diamidines have been found to possess antibacterial and antifungal properties. Only limited trials in bacterial infections have been reported because of the signal success of the newer antibiotics. The lack of therapeutic agents for the systemic fungal diseases, however, has led to further exploration of the aromatic diamidines in these diseases.

Elson[2] had demonstrated that the growth of many of the pathogenic fungi was inhibited by low concentrations of the diamidines. *Achorion schoenlenii*, *B. dermatitidis*, *Sporotrichum schenckii*, and *T. sulfureum*, for example, did not grow in the presence of 1–4 mcg of the diamidine per ml of medium. Seabury and Artis[3] showed that stilbamidine was fungicidal against *Histoplasma capsulatum* in a concentration of 100 mcg per ml. Neoarsphenamine did not show comparable inhibition until ten times this concentration was attained, while penicillin, streptomycin, and neostam had no effect. The antifungal activity of the diamidines was greater at the higher pH ranges while phospholipids and nucleic acids neutralized their fungistatic properties.[1]

The pharmacology of the diamidines has been previously reviewed.[1] There is an extensive clinical experience with the use of the diamidines. No fatalities have been noted when properly prepared solutions were employed, although immediate vascular reactions, local irritation at the site of injection, and a delayed stilbamidine neuropathy have been described.[1]

North American blastomycosis may be clinically manifested as superficial cutaneous lesions or as a systemic disease which is highly fatal. In general, treatment has been unsatisfactory with iodides, desensitization vaccine, x-ray, arsphenamine, cauterization, penicillin, or streptomycin when used singly or in various combinations. Four patients with systemic blastomycosis have received stilbamidine with beneficial response.[4, 5] In addition, propamidine 0.1 per cent solution was applied to accessible local lesions. Since fibrin and desoxyribonucleic acid are components of of inflammatory exudate, Streptodornase and Streptokinase were, when feasible, employed to remove these inhibitors of diamidine activity. A stilbamidine neuropathy appeared after a total dosage of 2.2 to 6 grams, in three of these four patients, one to four months after the completion of treatment.

It has recently been reported,[10] that two patients with systemic blastomycosis have been benefited by treatment with large amounts of aureomycin over a prolonged period of time. The sensitivity of the Blastomycetes to aureomycin was not great, and 10,000 to 40,000 mcg of aureomycin per ml of medium was necessary to inhibit the growth of B. dermatitidis.

The efficacy of stilbamidine in the treatment of systemic blastomycosis has been confirmed by others. One patient with actinomycotic infection, who had not responded to prolonged sulfadiazine and penicillin therapy, was cured when stilbamidine systemically, and propamidine locally, were employed.[4, 7]

Three cases of cryptococcosis (torula) infection showed no response to stilbamidine therapy. Experimental infections in mice were controlled when large doses were employed (250 to 500 mg/kg).

Parsons and Zarafonetis,[8] in their review of histoplasmosis, noted two patients who had received stilbamidine. One patient who was treated with neostam and stilbamidine was cured. Seabury[9] reported that two patients with histoplasmosis were only temporarily improved after stilbamidine therapy.

The further exploration of the diamidines for the therapy of systemic fungal disease is warranted in light of the *in vitro* susceptibility of various species of fungi and the uniform beneficial response noted in North American blastomycosis. It appears that *Cryptococcus neoformans* (*Torula*) and *Histoplasma capsulatum* infections are resistant to the concentrations of stilbamidine which can be attained clinically.

* Presented as the second of two papers in the Symposium on "The Diamidines in Pharmacology and Clinical Application," held by the Section of Biology on April 14, 1952.

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*SECTION OF MATHEMATICS AND ENGINEERING**

CONVECTION AND ZONAL ROTATION IN CELESTIAL BODIES†

By W. S. JARDETZKY‡

The fundamental problem in our understanding of the characteristic features of the Earth's crust (the actual distribution of continents and mountain chains) is to elucidate the mechanism which led to their formation.

It has been shown by the author (1929), that such a mechanism is found in the assumption that, during the formation of the crust the Earth was in a state of zonal rotation, and the principal characteristic of the distribution of angular velocities was the existence of an equatorial acceleration. Precisely this type of zonal rotation can be observed now on the Sun, Jupiter, and Saturn.

In a series of investigations (1929–1951), the author has been able to demonstrate how the hypothesis of zonal rotation yields an explanation for the formation of a single continental block during the first stages of solidification of the crust, and for the subsequent splitting of this block leading to the formation of continents, ocean basins, and mountain chains as we see them today. The conclusion that currents corresponding to a zonal rotation in the layer underlying the crust can produce deformations of the crust of the same type as the actual distribution of land and sea, has also been confirmed by the author's experiments (1948).

At that time, no attempt had been made to fix the nature of phenomena which will produce and maintain a zonal rotation, and this latter is the purpose of the present paper.

In the two simplest cases of zonal rotation of a fluid mass like a star or a planet, either the equatorial belt or the polar regions can be accelerated with respect to other parts of the mass. The various conditions under which a zonal rotation can take place have been the subject of a number of investigations (Jardetzky, 1935, and Wasiutynski, 1946).

On the other hand, O. Fisher (1889) seems to have been the first to point out that the existence of convection currents was necessary to produce certain tectonic phenomena. This idea was applied in several forms since that time (Schwinner, 1942, and Gutenberg, 1951). Solutions of particular problems were obtained, starting with special conditions concerning thermal disturbances, like the difference in temperature distribution under the continents and suboceanic parts of the crust, like a cellular convection of Bénard type, or like others. None of these theories of subcrustal currents, however, were able to explain the characteristic facts known about the formation of the crust, and have failed to show the mechanism of this process as a whole.

Recently, R. Daly (1951) suggested that the asymmetry of the uppermost layer of the Earth's crust is due to the action of the gravity pull of the moon-made tidal bulge of the molten Earth. Taken as a single fact, this horizontal segregation of the Sial can be explained by Daly's assumption as well as by the author's hypothesis of zonal rotation. Daly's objection to this hypothesis is

* A paper, by Dr. Thomas J. Haley, entitled "The Release and Identification of Blood Borne Vasotropic Substances After Whole Body Irradiation" was presented to a Special meeting of the Section of Biology on April 22, 1952. No abstract of this paper had been received at the time of publication.

† This paper, illustrated with lantern slides, was presented at the Section of Mathematics and Engineering on April 18, 1952.

‡ Department of Geology, Columbia University and Civil Engineering Department, Manhattan College, New York, N. Y.

that any zonal rotation postulated for a gaseous or gas-swatched Earth could not persist for long after the liquefaction had taken place. This objection could have been valid, if the increasing viscosity were the single operating factor, but there are other important factors to be taken into account, as well.

In the case of the Sun, a certain regularity of convection currents was considered by many investigators in order to obtain the Carrington-Faye law. It was suggested that the physical factors place in the crust. It seems highly probable that convective currents were maintained by energy sources in the Earth's interior during several geological periods, and that they were of the same kind as those in the other members of the solar system. Elsasser (1949) concluded that the Earth core, even now, rotates more slowly than the mantle. To explain the formation of the principal features in the Earth's crust we need but to assume such relative displacements in the Tertiary and preceding periods.

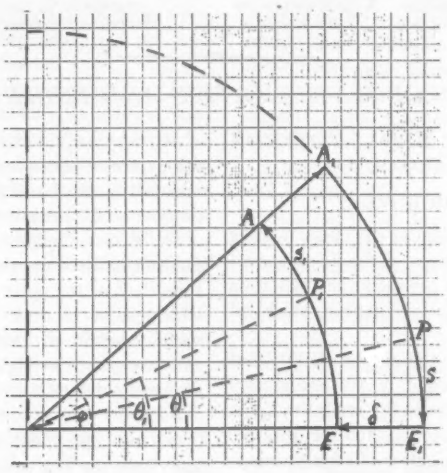

FIGURE 1.

maintaining the differences in angular velocities of rotation in celestial bodies are these convection currents themselves. They can be produced either by gravitational instability, by lack of thermal equilibrium, or by the viscosity of radiation. These factors are able to maintain a non-uniform rotation against viscosity. This, and the fact that even gravitationally stable layers cannot be generally in thermal equilibrium, was pointed out by Vogt (1925), Eddington (1925), and recently by Jeffreys (1951).

We have all reasons to assume the operation of the same factors in case of the Earth. The Earth is nothing but one of the celestial bodies. Assumption of gravitational or thermal equilibrium in the Earth is very useful in many theories, but that there was never exact equilibrium and thermal instability seems to have been a primary factor in a chain of mechanical phenomena which took

The question which now arises is, what direction of convection currents was predominant in the layer underlying the solid crust. Theoretically, various distributions are possible, but the most important are two, in which the convection currents occur symmetrically in two hemispheres, having their direction on the surface either toward the poles of a celestial body or toward its equator. Faye (1865) pointed out the importance of radial convection currents producing an equatorial acceleration on the Sun. Joukovsky (1885) proved, in an investigation concerning the motion of a solid body having a cavity filled up with a viscous liquid, that if the circulations at the surface of the liquid are directed toward the equator, the mean square of angular velocity increases from the center outward and *vice versa*. This case corresponds to the observed characteristics of rotation of fluid members in the solar system and can be utilized

in the explanation of the mechanism of the Earth's crust.

Thus, the hypothesis of convection currents in the Earth's interior and the hypothesis of zonal rotation can be brought into connection. The latter hypothesis makes use only of the existence of such a deviation from the type of rotation exhibited by a rigid body which is directed along the parallels. The former provides a physical basis for the explanation of this deviation, when it is taken in that form which was suggested in Astrophysics.

Taking the above case, in which there is a current rising at some latitude, moving along the surface of the liquid planet, and descending at the equator, we can now determine the direction of relative deviation by a few simple considerations. We assume that an isolated liquid mass begins to ortate about an axis with an angular velocity ω = constant, and that the convection currents occur at the same time. Let these currents be directed clockwise in the northern hemisphere and counterclockwise in the southern hemisphere in the meridian planes. The question is whether there will be a deviation of particles from these planes. We shall take on FIGURE 1 only the northern hemisphere. Let the circulation occur in a layer AA_1E_1E. Since we assume that the liquid body has a nearly spherical shape, this layer will be bounded by two circles. Let their radii be: $a = OE_1$ and $b = OE$. Then, the components of velocities perpendicular to the meridian plane will be at the initial moment $t = t_0$

at:	A	A_1	E_1	E	(1)
	$\omega b \cos \phi$	$\omega a \cos \phi$	ωa	ωb	

Let us assume that the particle A will reach the point A_1 at a moment $t_1 > t_0$ and that, at the same time, in the equator plane, the particle E_1 will reach E. Then, because of the convective current, particles located earlier at P and P_1 will have the new positions at E_1 and A respectively. Carrying their angular moments, the particles will have at the moment t_1 the velocity components as follows:

$\omega b \cos \theta_1$	$\omega b \cos \phi$			(2)
		$\omega a \cos \theta$	ωa	

where θ and θ_1 are the latitudes of the points P and P_1.

The differences in velocities at the points E_1 and A_1 before and after these displacements are:

$$[V_{E_1} - V_{A_1}]_{t_0} = \omega a(1 - \cos \phi),$$
$$[V_{E_1} - V_{A_1}]_{t_1} = \omega (a \cos \theta - b \cos \phi) \tag{3}$$

To see, immediately, the effect of the changes, we assume that the thickness of the layer in which the circulation occurs

$$\delta = a - b = s = s_1 \tag{4}$$

is very small. Then we can put

$$\cos \theta = \cos \frac{s}{a} = 1 - \frac{\delta^2}{2a^2} \tag{5}$$

and

$$[V_{E_1} - V_{A_1}]_{t_1} = \omega a(1 - \cos \varphi) + \omega \delta \cos \varphi - \omega \frac{\delta^2}{2a}. \tag{6}$$

The last term is less than the antecedent until $\cos \phi$ becomes smaller than $(a - b)/2a$. If the thickness (4) of the layer in which the circulation occurs is small, as we have assumed, this condition will hold for convective currents rising even at high latitudes (ϕ). Then,

$$[V_{E_1} - V_{A_1}]_{t_1} > [V_{E_1} - V_{A_1}]_{t_0}. \tag{7}$$

In a similar way we obtain from the figure that:

$$[V_E - V_A]_{t_1} > [V_E - V_A]_{t_0}. \tag{8}$$

Thus, the displacements caused by a convective current, under conditions mentioned above, tend to produce an increase in both differences (7) and (8), *i.e.*, on two boundary spheres of the layer in which the circulation occurs. This variation of velocity components perpendicular to the meridian plane at every point means certain changes in angular velocity. The increasing difference (7) shows, then, that compared with the case ω = constant a particle at the equator has to be accelerated with respect to those at the latitudes different from zero and on the same surface.

These simple considerations illustrate once more the probable nature of zonal rotation in a celestial body.

Our conclusions about the possible effect of the zonal rotation of a celestial body on the formation of its crust are quite general, *i.e.* then can be applied to every planet or star which begins to solidify because of cooling. As to the Earth, two more conclusions should be pointed out.

During the process of continent formation, the Earth's crust became a solid shell (covering first only a part of the surface), on the interior side of which the currents of magma produced stresses under those parts which formed the bottom of the oceans as well as under those which gave rise to continents. Thus, in the theory given by the author, there is no necessity to make use of the concept of the so-called "continental drift." The deformations resulting from forces of zonal rotation are investigated as occurring in the shell as a whole, and two of them found to be of foremost importance: the horizontal displacements of shell parts (sub-oceanic as well as continental) dragged by magma, and the folding at those places which are determined by the distribution of forces due to a zonal rotation.

The second point concerns the surface patterns resulting from the horizontal displacements. Theoretically, there are several possibilities in which the rupture of the shell could occur as a resut of a zonal rotation. Previously published experiments of the author show that the pattern resulting from a solid plate subjected to zonal deformation by an underlying plastic mass will also depend on the heterogeneous structure of the plate. As might be expected, splitting will be favored in areas in which the plate is thin or weak, and prevented in those of considerable strength. Taking into consideration the fact that the striking similarity to the actual distribution of continents and mountain chains was accentuated in those of the experiments in which areas of thickening were so selected as to correspond to the distribution of shields, the author would suggest the conclusion that the existence of shields was the second factor which, together with the law of zonal rotation, determined the number, position, and shape of the existing continents.

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SECTION OF PSYCHOLOGY

ANXIETY AND OTHER FEELINGS*

By HOWARD LIDDELL†

In mulling over the subject chosen for the panel discussion, I was forced to consider how an experimental biologist, engaged in the investigation of animal behavior, could contribute to the discussion of a topic essentially psychological. Upon further reflection, however, I discovered that almost my whole career as an investigator of conditioned reflexes in the sheep and goat had, in fact, been focussed upon the problems of anxiety and emotion. As a teacher of medical physiology, but as a student of behavior, many years went by before I recognized Pavlov's methodological error in assuming behavior to be but one special problem for the physiologist, in the sense that renal function or the motility of the gut are special problems requiring the mastery of refined skills. One's thinking becomes skill-centered, and although the method of the conditioned reflex seems simple, it is really difficult. In my own case, I derived great satisfaction in getting the best possible

* This paper was presented as part of the panel discussion on Differences Between Anxiety and other Feelings, at the meeting of the Section of Psychology on April 21, 1952.

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kymograph records of conditioned reflexes by including in such records more and more samples of bodily functions as modified by the training routine. In this quite natural way, my conditioned sheep and goats became for me animal preparations to be studied in the laboratory with the aid of controlled stimuli and the complex equipment for graphic registration of their responses. With so limited and concentrated an interest, I failed to regard my animal subjects as "case histories."

First of all, let me state explicitly the premise upon which my remarks will be based. I am assuming that the investigation of behavior, either clinically or experimentally, is an autobiographical pursuit. Both physician and experimental behaviorist lead many lives. Each leads his own life but he also, by empathy, leads the lives of his patients or animal subjects. This empathic and vicarious living through of another's experiences provides the investigator with a store of manipulative knowledge. Thomas French* has clearly stated what is meant by manipulative knowledge. The physician is listening to the patient's account of his difficulties when suddenly something just said strikes him as peculiar. He inquires about this "something" and, when he learns more of the emotional context of the patient's behavior, the peculiarity becomes natural and understandable.

This intuitive working through of a behavior problem, French regards as the essential preliminary to a deliberate scientific formulation.

In my own experience, when I have observed the same sheep or goat for the usual hour in the laboratory, day after day during conditioning, I often have the experience of witnessing behavior which seems peculiar; and, just as in the case of my psychoanalyst friend Dr. French, I find it necessary to scrutinize repeatedly the animal's behavior under various experimental conditions until this peculiarity seems natural sheep or goat behavior, in view of the laboratory of stresses to which it has been subjected. What language is one to employ in reporting the case history of his experimental animal?

If the description of the animal's behavior is to be meaningful, and not an exercise in symbolic logic, one must employ the words by which we communicate our own intentions, feelings, and emotions to others. It should occasion no embarrassment or feelings of guilt frankly to admit that such words as anxiety, anger, or fear are by inference, and by inference only, applicable to the animal's behavior.

Each animal's behavior from birth to death may be thought of as the unfolding of a plot. When we come to man, the plot thickens. The impatient reader may turn to the back of the book to see how the story comes out before returning again to its gradual unfolding. If we assume that there is a master plot, variations of which are portrayed by every mammal from birth, whether human or infrahuman, it is the delineation of this master plot or pattern which is the basic objective of our behavior science. Our science of behavior is one science—not two.

Nevertheless, I firmly believe that we, in the animal behavior field, cannot ever arrive at a definitive dynamics of behavior alone and unaided. At every step, we must rely upon the contemporary formulations of psychodynamics, although we ourselves are not engaged in research in psychodynamics.

Our animals cannot talk to us, that is, they cannot communicate with us at the conceptual level. At all times in our own proper research, therefore, we need and must rely upon the insights gained from studies of human behavior, based upon the painstaking microdissection of human experience by the psychoanalyst or other similarly trained specialist.

This is not the occasion upon which to give a documented report of our laboratory studies. I now appreciate, however, that for many years my investigation of conditioned reflexes and experimental neuroses in the sheep and goat have been aimed at attempting to disclose the animal origins of human anxiety.

In order to view the subject under discussion in historical perspective, we must cast our thoughts backward at least one scientific generation to the three great revolutionists of our science of behavior: Pavlov, Cannon, and Freud. All three of your discussants have met in the flesh one or more of these medical worthies. In my own case, I knew Pavlov and Cannon. Freud, I never met. To employ the nomenclature of genetics, Drs. Hoch, Rado and myself belong to the F_1 generation descending from the classical researches of Freud, Pavlov, and Cannon.

To my mind, their three great discoveries—the conditioned reflex, the emergency reaction, and

* French, Thomas M., 1952. The Integration of Behavior. University of Chicago Press.

the unconscious—are fundamental to our present understanding of human anxiety.

I venture to assert, on the basis of my own researches, that every conditioned reflex elicited by the employment of Pavlov's classical method is a manifestation of Cannon's emergency reaction; but a reaction in preparation for a disturbing state of affairs of which the animal has been duly warned by the experimenter's signal (or conditioned stimulus). This emergency, he must shortly face. It is the exquisitely refined control of the temporal intervals between one emergency reaction and the next that distinguishes the situation of the animal subjected to classical conditioning from the situation of Cannon's cat being barked at by a dog. Cannon's cats did not become experimentally neurotic. Animals subjected to classical conditioning regularly do so.

In respect to the second part of our assignment this evening, *viz.* other feelings, I can make only the following oblique statement. Even under carefully controlled laboratory conditions, there is a bewildering diversity of manifestations of the emotional reaction in our sheep and goats. We cannot so easily anthropomorphize these manifestations, as we regularly do with our family dog.

The preservation or continuance of such manifestations after the exciting cause has been removed, is, in my opinion, the behavioral equivalent in simple farm animals of clinically recognizable anxiety in the patient.

In conclusion, I will ask two questions. Is the notion of the unconscious a purely psychological concept? Is the unconscious biologically meaningless? For the answer to these queries we must refer to Dr. Rado and Dr. Hoch. At present, however, I am privately, even secretly, leaning to the view that the unconscious is not a purely psychological concept or working notion, and that the unconscious is coming to have practical meaning for the experimental biologist in his investigations of behavior.

DIFFERENCES BETWEEN ANXIETY AND OTHER FEELINGS*

By PAUL H. HOCH†

Three questions were asked of the panel discussants: (1) How can the difference between anxiety and other feelings be defined? (2) How can differences between anxiety and other feelings be recognized objectively in the human and animal organism? (3) How are differences between anxiety and other feelings expressed subjectively?

How can the difference between anxiety and other feelings be defined? In order to define feelings accurately, it would be necessary to know their basic origin. This is still obscure, however, and our knowledge about the different emotions is more descriptive than genetic. As inner mental conditions, emotions are quite indescribable. "Their relationship to the objects which prompt them and the reaction which they provoke are all that one can put down." (William James, 1892.)

The classification and subdivisions of emotions are manifold, but none of them are satisfactory. As to their genesis, no agreement has ever been reached, and the question remains: "Do the emotions produce bodily changes accompanying them or *vice versa*?" It is being realized more and more, however, that emotion is as much of an organic force as other somatic manifestations and that the "spiritual" functioning of the organism is inevitably tied to this organic substratum. An emotion is not possible without its "body feeling." Actually, emotions are only felt in the body. A disembodied emotion is an intellectual construction, but has no feeling quality. The varieties of an emotion are innumerable. We also know some of the physical manifestations of the basic or coarse emotions like anxiety, but none of the more subtle ones such as asthetic or moral feelings, which are intimately linked to the highest symbolic functions of the mind.

If we strip these feelings from their subjective meaning to the organism and study them simply as tension phenomena, methods of physiology can be used in their appraisal. This becomes impossible, however, when we begin investigating the meaning of this emotion to the organism whic moves on a symbolic level. These symbolic values can only be expressed today in a general fashion and not in any of the following physiological terms, for example: receiving a stimulus; responding emotionally; becoming tense under the impact of it; showing excitatory and inhibitory manifestations,

* This paper was presented as part of the panel discussion on Differences Between Anxiety and other Feelings, at the meeting of the Section of Psychology on April 21, 1952.

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and also manifold discharge phenomena. Physiological changes, of course, are present in all feeling, but their registration in the subtle emotions is not solved. All emotions can be basically classified, however, as tension-producing or tension-discharging (anabolic or katabolic) manifestations. They indicate a change in equilibrium of the organism. They serve as adaptative functions in relationship to alteration of the homeostasis from within and without. Most of the emotions, but not all, are in relationship to some striving of the organism. Love, hate, pride, hope, joy, shame, grief, rage, and anger occur in relation to some object. We are dealing here with motivated alterations of equilibrium. This object motivation appears in great variety and also the emotions connected with it. The differentiation of the emotions from each other is based more on the motivational object relationship than on the physiological changes which are very similar in different emotions. We actually register more alterations of the equilibrium on a physiological level, in general, than changes which are specific for one emotion.

How can differences between anxiety and other feelings be recognized objectively in a human or animal organism by an observer? We recognize these differences by the expression of the feeling on a motor level. The slower breathing, trembling, and paleness of the fearful is different from the state of rage, with its deep breathing, flushing of the face, dilation of the nostrils, and clenching of the teeth, or the state of grief with its tears, sobs, *etc.* To be able to objectivate these emotions by observation depends not only on the quality, but also on the quantity of the emotion present. If the emotion is strong enough to express itself on a level of preparatory moves for action, then the different and especially mimetic motorizations enable us to recognize the special emotion present. If the emotion is not strong enough, we discern only a certain tension, but we are not able to diagnose the feeling present. Inhibition of an expression of an emotion is very common. If the emotion is strong, the inhibitory force does not work as well as when the quantity of the emotion is not as marked.

In the realm of the refined, more subtle feelings, we are not able to make any differentiation based on observation without having a statement from the person who feels them. For instance, it is difficult to differentiate by observation alone if the person is anxious, timid, irresolute, and doubtful. All of these have a common factor which has anxiety roots. Nevertheless, the different shadings are of importance.

We can only use specific somatic correlations in the elementary emotions like anxiety, anger, and depression. In such cases, very often the registration of the emotion in the vegetative nervous system (because we do not have registration in the central nervous system) is very similar in all emotions. For instance, fright and rage are able to produce the same adrenergic and cholinergic responses in both.

How are differences between anxiety and other feelings experienced subjectively? From a practical point of view, the differentiation between elementary emotions, (*i.e.*, anxiety, rage, and depression), is fairly reliable. The more refined the emotion gets, the less clearly defined it becomes, not only objectively, but also subjectively. Nevertheless we have to call attention to the fact that, seemingly, the elementary emotions are also feeling composites. Their elements, however (the "molecular" structure) are unknown. They are subjectively differentiated from each other by different feeling patterns.

A depressed person, for example, feels a lack of energy, apathy, lack of interest, loss of libido, retardation, indecision, feeling of insufficiency. At times, he also feels tense, agitated, and even anxious. Some of these feelings also occur in anxiety and *vice versa*. They are, however, differently grouped. Indecision and lack of interest is also present in some who suffer from anxiety, but these persons lack the feeling of "blueness." When angry, the aggressive feelings predominate to subdue or annihilate the opponent and, while apprehension and even fear often enter into aggression, feelings grouped toward fight and not flight (anxiety) are predominant.

In jealousy, a complex feeling of anxiety of losing the loved person is mixed with hostility toward the same person. All these feelings, therefore, can occur in a mixed form and, as a result, differentiation becomes very difficult. Some of the emotions become clearer when the motives for their genesis, and the psychodynamic constellations in which they occur, are investigated. Here, psychoanalytic exploration often shows that fear is underlying aggression, depression, or even elation, as specialized defense mechanisms which the ego uses to cope with overwhelming upsetting stimulation. In some analytic contributions, however, this principle has become so over-elaborated that one emotion is always explained by another;

for instance, that they are all sexual in origin or that aggression is always externalized fear (you are anxious because you are aggressive, or you are aggressive because you are anxious). This is sometimes true, but it is not always so. The following question arises: Do emotions like aggression, jealousy, paranoid feelings, and depression derive from anxiety or are they primary emotions.

In recent experimental investigations with drugs like mescaline, it was possible to produce intense anxiety in some persons. When the anxiety reached a high degree, mechanisms suddenly occurred which were depressive, aggressive, and paranoid, indicating that if anxiety reaches a certain quantity, other emotional mechanisms are mobilized which are seemingly derived from anxiety. On the other hand, depression and aggression are also observed without a display of anxiety. Further research will have to clarify whether or not anxiety is the starting point.

ON THE PSYCHOANALYTIC EXPLORATION OF FEAR AND OTHER EMOTIONS*

By SANDOR RADO†

Since, in my opinion, we cannot meaningfully split off so-called anxiety from the entity of fear, I should like to present the topic under consideration in terms of fear.

In adaptational psychodynamics, we do not study fear as an isolated phenomenon, as a feeling in and of itself. We study fear mainly by the method of contextual inference.[4] The over-all context in which we seek to understand fear is the interaction of organism and environment. We begin with the everyday observation that fear is a response to danger. So is pain, and so is rage. Each of these responses in turn prompts the organism to further activities designed to prevent and repair damage to its organic integrity. We call the context of activities concerned with danger, emergency behavior.[5] This designation was inspired by the work of Walter B. Cannon.[1]

I have attempted to show elsewhere that the organization of emergency behavior is hierarchically ordered and reflects the course or evolutionary history. In this organization, pain is the warning signal of damage Though pain and damage are not inevitably connected, nevertheless, their linkage is so frequent and dependable that the organism can use pain effectively as a warning signal of damage. This signaling arrangement, developed at an early stage of evolutionary history, is the very basis upon which the entire organization of emergency behavior has evolved. In the further course of evolution, as more and better equipment appeared, the range of foresight (expectancy of pain from damage) increased, and so also, through the cumulative effect of repetition, did the automatization of operating patterns.

At a low evolutionary stage, equipped only with contact receptors, the animal cannot yet foresee the next situation it will meet. Nevertheless, its behavior already reveals a minimum degree of foresight. When pained it makes every effort to rid itself of the source of suffering, as if expecting that otherwise the pain will continue. This elementary characteristic of all animal existence was noted by Charles Darwin: "Great pain has urged all animals during endless generations to make the most violent and diversified efforts to escape from the cause of suffering."[2]

I termed these activities elicited by pain the riddance response.[3] This response is ingrained in our organization. Such reflexes as scratching, shedding of tears, sneezing, coughing, spitting, vomiting, and colic bowel movement, are riddance reflexes, designed to eliminate pain-causing agents from the surface or inside of the body.

Repression is automatized riddance from painful thought and feeling. Moreover, inhibition of motor activity that has become dangerous also is automatized riddance.

At subsequent stages of philogenetic history, there evolved the distance receptors, whose adaptive function we may best characterize in Sir Charles Sherrington's words: "The animal's locomotion carries it with one end foremost and habitually so. That leading end, the head, has receiving stations signaling from things at a distance, things which the animal in its foreward movement will next meet. A shell of its immediate future surrounds the animal's head."[7]

Exploration of this shell by the distance receptors enables the animal to foresee pain from an

* This paper was presented as part of the panel discussion on the Differences Between Anxiety and other Feelings, at the meeting of the Section of Psychology on April 21, 1952.

† Columbia University Psychoanalytic Clinic, New York, N. Y.

impending damage. Clearly, fear is a warning signal elicited by this expectancy. The same applies to rage. These two emergency emotions in turn spur the organism to muscular activities, but of the exactly opposite direction and kind. The response to fear is escape (flight), and to rage, combat (fight). Clinical observation indicates that fear is an immediate response to the threat of pain from damage, but rage is not; it looks as if the organism has to be primed to rage by a shot of fear. Moreover, the organism is often seen to oscillate between fear and rage until one or the other prevails.

The emotionally aroused animal's muscular activity, however, is not limited to escape or combat. Already at this evolutionary stage there begins to develop the outward display, or more precisely, the expressive aspect of these emotions, presumably for the purpose of broadcasting the warning to the other members of the herd.

With the further evolution of the central nervous system, in particular of the cerebral cortex, intellectual activity rose from an adjunct to the emotions to a super-imposed organization of growing complexity and significance. In its highest forms, freed more and more from the influence of the emotions, thought became an exploratory tool of ever-increasing dependability. With the aid of this tool, man learned to calculate and foretell dependably events lying beyond his "shell of the immediate future" and has thus vastly expanded the spatial and temporal range of his expectancies.

However, between emotion, on the one hand, and unemotional thought, on the other, there is the intermediate level of emotional thought. At this intermediate level, emotion still tends to control reason rather than the other way around. By comparison with unemotional thought, emotional thought is an inferior instrument for the interpretation of what one is actually exposed to. It is not objective but selective. It tends to justify, and thus to feed, the emotion from which it springs, and by which it is controlled.

At the intermediate level of emotional thought, brute fear and rage are in a measure "humanized," *i.e.*, softened down to apprehensive thought and angry thought. There is more discrimination, analysis, combination, and greater flexibility and diversity of motor performance. At the high level of unemotional thought, the organism responds to danger with a purely intellectual expectancy of pain from threatening damage. Unhampered by the emergency emotions, the intellect safeguards the organism in the superior manner of a computing machine. Yet, the moves prompted by these new sets of warning signals remain substantially the same: escape on the one hand, and combat on the other.

In the infant and in the helpless, fear tends to elicit a cry for help. In social dependency relationships, escape may take the form of submission to the authority; and rage, that of defiance.

During cultural history, long before the stage of unemotional thought was attained, there developed those more complex elaborations of fear known as fear of conscience and guilty fear. Fear of conscience elicits conscious restraint, or automatic repression of dangerous thought and desire, and automatic inhibition of dangerous action. Guilty fear, on the other hand, elicits the reparative pattern of expiatory behavior, a pattern often complicated by rage retroflexed and vented on the self.

In order to place the theory just outlined in the proper perspective, let me remark here that in adaptational psychodynamics we contrast the emergency emotions with the welfare emotions, such as strong desire, joy, love, and pride.

After this theoretical preparation, we may now proceed to the methodology of actual psychoanalytic work with the patient. How do we detect in him the presence of fear, or for that matter, of any other emotion?

We listen to the patient's running account of his life performance, observe his treatment behavior and, aided by the technique of free association, trace the patterns of his thoughts and actions. We know the characteristic patterns of emotionally-inspired thought and action (we learned them by advancing from the simple to the complex, from the crude to the refined, from the open to the hidden) and can readily infer from the emerging patterns the emotions that inspired them. We thus detect the presence of fear and other emotions by inference from their motivating (integrative) action, that is to say, by inference from the behavior context. I must add, however that the drawing of such inferences is not a purely intellectual process: the investigator is guided therein by his own emotional resonance. The gross manifestation of resonance is known in everyday life as the contagiousness of emotions. In this procedure of exploration by inference, the expressive aspect of the patient's emotion and even the

patient's subjective feeling, which he may describe to us, are often enough used only as controls. Our theory reflects this exploratory procedure. In general, we view the emotions as a class of instrumentalities of the organism for the integration of its behavior.

Clinical experience conclusively proves that the feeling aspect of fear or of rage may be completely absent, as we say, removed from the patient's awareness by repression, and yet the emotions of fear and rage may nonetheless be present in the organism and exert their motivating (integrative) influence on the patient's actions and thoughts. In these instances we speak of unconscious, or better, of non-reporting fear and rage.[4] Sometimes, but not always, the presence of such non-reporting emotions is also indicated by a feeling of qualitatively undifferentiated tension.

The patterns of thought and action motivated (integrated) by the various emotions characteristically differ from one another. We speak of escape pattern, combat pattern, submission pattern, defiance pattern, brooding pattern, expiatory pattern, pattern of self-damaging defiance, *etc.* Hence, the same method of contextual inference also enables us to tell the various emotions apart.

We now have our answer to the first two of the questions posed for this panel discussion. First: the differences between fear and other emotions can best be defined by their motivating (integrative) action. Second: these differences can be objectively recognized by examining the patterns of the patient's actions and thoughts.

As we see, the contextual study of the emotions dwarfs the significance of their feeling aspect. This is most fortunate indeed, because we have no dependable means for the comparative study of other people's feelings. Even our capacity for understanding the feelings they describe depends on our own emotional experiences. This answers the third question posed for this panel discussion: though the subjective differences between emotions, say between fear and joy, are of overriding importance for our well-being, the scientific study of the verbal accounts of these differences in feeling is still in an elementary stage. We speak of differences in "specific feeling quality," hedonic tone (pleasant–unpleasant), intensity (mild–strong), *etc.*

Let me call your attention to an important difference between feeling and thought. Though both belong to the private phase of behavior, the patient can communicate his thought verbatim, but he cannot communicate his feelings directly. This is why emotionally-inspired action is so helpful to the investigator: it moves the emotion from the private phase to the public phase of behavior. Moreover, emotionally-inspired thought is often enough fantasied action and hence renders the investigator a similar service. From the point of view of the investigator, emotionally-motivated action and emotionally-motivated fantasied action act as amplifiers of the motivating emotion.

The theory of emergency behavior proves helpful in clarifying the variety of pathological fears and other faulty emergency responses encountered in psychoanalytic work. The patient is seen to develop fear in the absence of danger, to respond with excessive fear to trivial danger, to suffer from guilty fear arising from imagined guilt, *etc.* His fear may become so severe that its inhibitory action defeats its emergency function, and damages, rather than aids, the organism. When fear thus becomes a threat to the organism it elicits a new round of preventive and reparative measures which often enough miscarry completely. I termed the resulting disturbance emergency dyscontrol. This disturbance may include the simultaneous arousal of fear and rage, which then compete with one another for immediate discharge, and thus create a discharge interference.[6] In obsessional cases, this is seen in the see-saw of the patient's broodings and in the see-saw of his rituals. In great psychotic excitement, with the breakdown of hierarchic regulation, the contrasting action patterns elicited by simultaneous fear and rage may produce a pattern of motor confusion. So far, clinical observation has fully justified the proposition that failures of emergency adjustment lie at the bottom of disordered behavior.

The theory of emergency behavior depicts an exceedingly complex subject in first approximation. But it organizes facts scattered over vast areas under a common point of view, and points up ever new problems that can be explored by observation and experiment. Without a fruitful conceptual scheme we could undertake neither research nor treatment.

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SECTION OF OCEANOGRAPHY AND METEOROLOGY

SOME PROBLEMS CONCERNING THE DYNAMICS OF THE GULF STREAM*

By GERHARD NEUMANN†

The great ocean current which dominates the circulation of the northern part of the North Atlantic Ocean is called the "Gulf Stream System." It includes the whole northward and eastward flow beginning at the Straits of Florida. Following the East Coast of North America, it first leaves the continental shelf off Cape Hatteras, and continues in various branches and whirls while crossing the ocean. In oceanography, the term "Gulf Stream" is specifically used for the part comprising the section of the system between Cape Hatteras and the region east of the Grand Banks, in about 45° West, where the stream begins to branch out.

In this paper, we shall apply the term "Gulf Stream" also to the midsection of the stream system in the central part of the North Atlantic, *i.e.*, the "North Atlantic Current," whose branches at the surface are often masked by shallow and variable wind drift movements. Therefore, the current system is usually more clearly recognized just beneath the surface layer of the wind-stirred water.

This important ocean current has been described and explained in different ways during the history of its exploration. As to our empirical knowledge, it should be understood that the progress is closely related to the progress in the technique of oceanographical observations and methods. During the last years, Spilhaus (1941)),[1] Iselin (1948),[2] and Fuglister *et al.* (1951)[3] have made detailed surveys of the Gulf Stream with new instruments and techniques, which made it possible to obtain a nearly continuous picture of the temperature distribution with depth and current recordings.[4] Several cruises of the "Atlantis," using these new methods, have established without doubt the striking narrowness of the Gulf Stream, which has been defined as a continuous band of a narrow swift current reaching from the continental shelf off Cape Hatteras to about 50° W., where the stream forks into three or more branches. The measurements furthermore revealed considerable changes in the position of the main-axis of the Gulf Stream.

Going farther to the east, we may refer to the observations of the International Gulf Stream Expedition (I.G.E.) in 1938. These observations also indicated the existence of narrow currents, often separated by weaker counter currents in the area between 30° W. and 40° W. northwest of the Azores.[5, 6] The formation of more or less narrow currents, therefore, seems to be not only a particular property of the current along the East-Coast, that is of the Gulf Stream between Cape Hatteras and the Grand Banks, but of the stream system all over the ocean and, with certain exceptions of probably the ocean currents in general.

The dense network of stations obtained in May and June, 1938, by the I.G.E., in a region of less than 100,000 square miles, revealed irregularities in the stratification of the ocean water down to a depth of about 2,000 m, which can be compared with the results of the last "Atlantis" cruises. The narrowness of the current branches is of the order of magnitude of 40 to 60 miles from the current axis toward the northern and southern border. Some of the observed features in the flow may be due to the influence of the bottom topography, according to W. Ekman, but the main feature seems to be related to a characteristic flow pattern of ocean currents in stratified water in general; that is, the tendency of moving water masses to form narrow swift currents between more homogeneous water types in a horizontal direction. A similar mass distribution, as obtained by the sections of the I.G.E., shows the "Atlantis" section north of the Azores along 30° W. in 1931 according to Iselin (1936).[7] This tendency

* This paper, illustrated with lantern slides, was presented at a meeting of the Section of Oceanography and Meteorology on March 25, 1952.

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is indicated also in an "Atlantis" section along the meridian of 41° W. as represented in FIGURE 2.

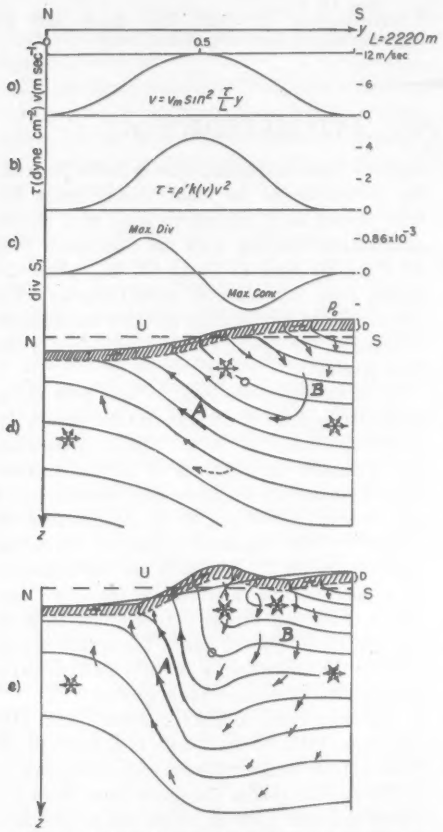

FIGURE 1. Schematic representation of a meridional cross section through a zonal current in stratified water. (a) Zonal wind velocity distribution. (b) Distribution of the wind stress as derived from (a). (c) Zonal distribution of divergence of the water mass transport S_i in the layer of frictional influence D. (d) Schematic cross section showing the slope of the sea surface, the lines of equal density, and the lateral and vertical circulation by arrows. The "arrow-asteriks" indicate regions of predominating isotropic mixing. The wind-induced geostrophic current is directed perpendicular into the plane of the figure. The shaded surface layer of thickness D means the layer of frictional influence, and the zone of maximum upwelling is indicated by U. (e) Cross section representing the final stage as given by the combined geostrophic equilibrium—and the austausch equilibrium-condition. The main current perpendicular into the plane of the figure is concentrated in the region of heavy arrows south of the zone of maximum upwelling U.

This "front-watertype" character of moving ocean water cannot be a stable pattern. The dynamic feature of the upper layer of the ocean, that is, the layer of several hundred meters, or at higher latitudes, of 2,000 m. and more, is mainly induced by the atmospheric circulation. More precisely, it must be said that it is induced by the mean surface wind, averaged over some days or weeks. This time depends upon several factors, such as latitude, stratification of the ocean, and the depth of the wind-induced gradient current. The deep-reaching wind-generated ocean currents (such as the Gulf Stream) have to be considered as "integrators" for the wind effect at the sea surface.

From the theoretical point of view, a series of papers have been published during the last years on the nature of ocean currents driven by broad steady wind systems.[8, 9, 10] These interesting theories, although concerning ocean currents in general, can be considered partly as a theoretical approach to the problem of the Gulf Stream, and as a remarkable step in dynamic oceanography.

The new observations present us with a more complicated picture of the large scale flow, as might be expected. Conspicuous features of the ocean currents, especially of the Gulf Stream, are not explained by the present theories. As pointed out already by Munk and colleagues (1950),[11] there are some essential features in the dynamics of the Gulf Stream which have not yet been recognized, and this probably will be the same with the general dynamics of ocean currents.

The problem is as follows: At the surface of an enclosed sea, the wind exerts a certain stress. The boundary conditions are that the current follows the shore line, and that no current component occurs perpendicular to the boundary. The question, therefore, is what current system results in such a basin under the given conditions?

Present theories start with a two-dimensional flow, and the basic differential equation is essentially a vertically integrated version of the vorticity equation. It expresses a balance between three torques: the lateral stress torque, the planetary vorticity, and the wind curl. With the boundary conditions, this differential equation leads to the result that the vertically integrated mass transport is different from zero only in the case where the curl of the wind stress vector does not become identically zero. Thus, in the case of an homogeneous wind field (uniform wind over the sea), no mass transport at all would occur. This result, naturally, does not imply that no currents are present. Nothing is said about the currents at all. We know also that, in an enclosed sea, the tangential stress of the wind causes and maintains a certain current system, which depends upon the depth. That this fact is not included

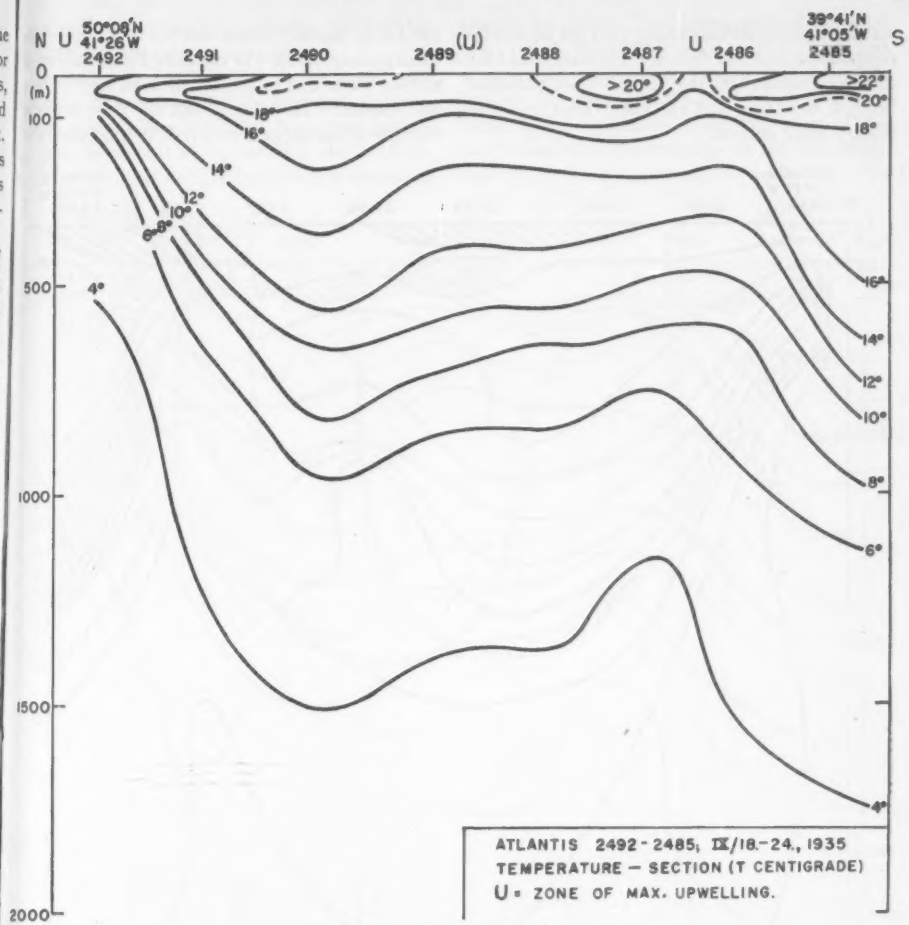

FIGURE 2a. Temperature section

in the theoretical results is explained by the simplifications implied in the vertically integrated two-dimensional equations, because the results otained do not present details of the current field, and, especially, they do not give the dependence of currents with depth. Therefore, we have to be careful when generalizing theoretical results based upon certain assumptions, and when drawing general conclusions from a restricted theoretical model. The solutions so far obtained are enjoined upon conditions which are not quite consistent with the physical nature of the problem, and with the question stated above.*

This inconsistency is the result of disregarding the three-dimensional nature of ocean currents, *i.e.*, neglecting vertical motion. The compensation of water masses, set into motion by a stationary wind stress, is not only attained by horizontal motions, but also (and apparently to a major part, at least at the boundaries) by vertical velocity components. There is no doubt that, generally, the vertical velocity can be neglected

* In the case of vanishing friction, it follows from the two-dimensional theory that the curl of the wind stress is compensated only by the variation of the Coriolis force with latitude. Increasing friction results in an eastward displacement of the subtropical gyre-axis and it is seen that, with increasing friction, the influence of the variation of the Coriolis force with latitude decreases. The author agrees with the result of Stommel (1948) concerning the effect of earth rotation on the westward intensification of ocean currents qualitatively, but the question is, how are the results changed quantitatively, when taking three-dimensional motion into account, as it is briefly suggested on the following pages.

when comparing its magnitude with the horizontal components, but this does not necessarily hold for the accelerations and the vertical mass transport between the lower and the upper limit of a stationary ocean current.

the I.G.E. started with a method first applied by Montgomery (1936)[12] to compute the transport of surface water due to the actual wind system over the Atlantic. In order to find the divergence of the flow in the uppermost layers, it is necessary to

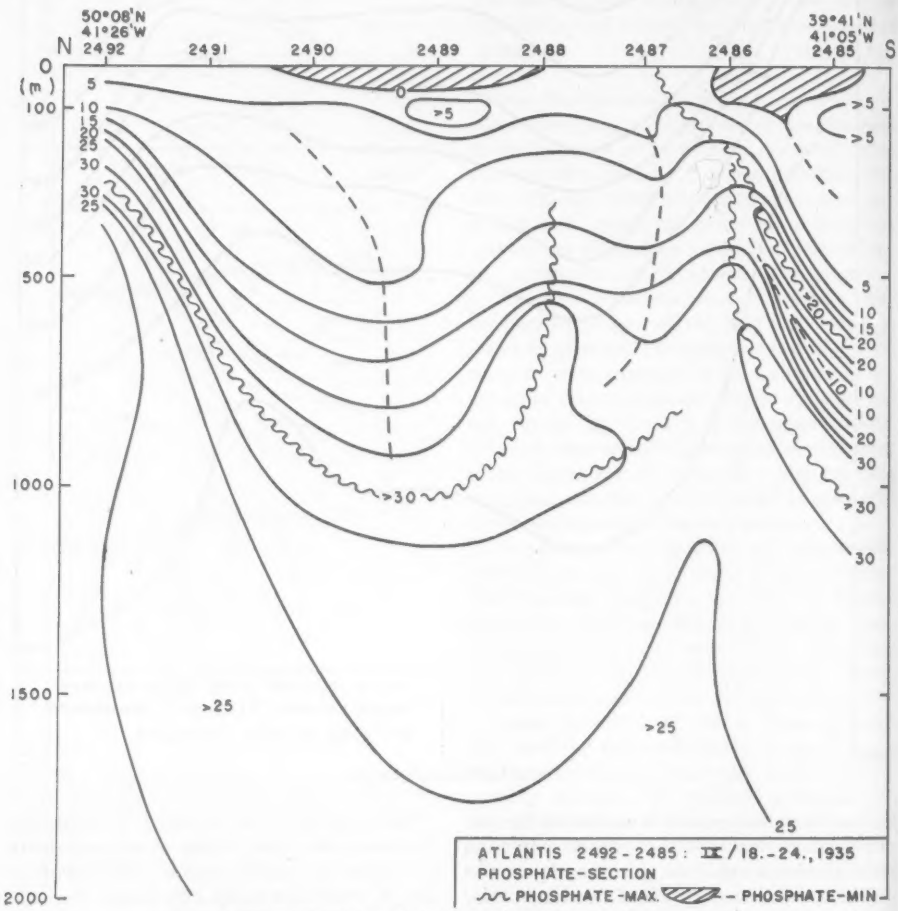

FIGURE 2b. Phosphate section (phosphate phosphorous, mg P per m²)

The observations of the I.G.E. clearly revealed a complicated system of converging and diverging flow in different levels of the investigated area, connected by vertical motions. The order of magnitude of the vertical velocity component was found to be about 2.10^{-3} to 3.10^{-3} cm sec^{-1} in the regions of maximum divergence. The attempt to explain the observed flow pattern of the Gulf Stream during the period of observations of

take into account both the wind stress distribution, in as much detail as possible, and the latitude. It cannot be the purpose of this paper to go into details of these calculations, or to discuss some special results of the I.G.E.* Let us consider here the effect of the wind stress, however, and

* An analysis of the observations of the International Gulf Stream Expedition is being carried out at present by the author at New York University.

the possible resulting currents in the region of the Gulf Stream in a more general way.

We assume a simple model, *i.e.*, a zonal wind field over the ocean beyond the influence of coastal effects, where the wind blows from west toward the east, being zero at the northern and southern border of the wind field, and attaining a maximum toward the south. The consequence of the wind effect is a divergent flow in the northern part, and a region of convergence in the southern part, because the mass transport by wind is proportional to the wind stress. The divergence of this mass transport is proportional to the curl of the wind stress (τ) and can easily be computed. The

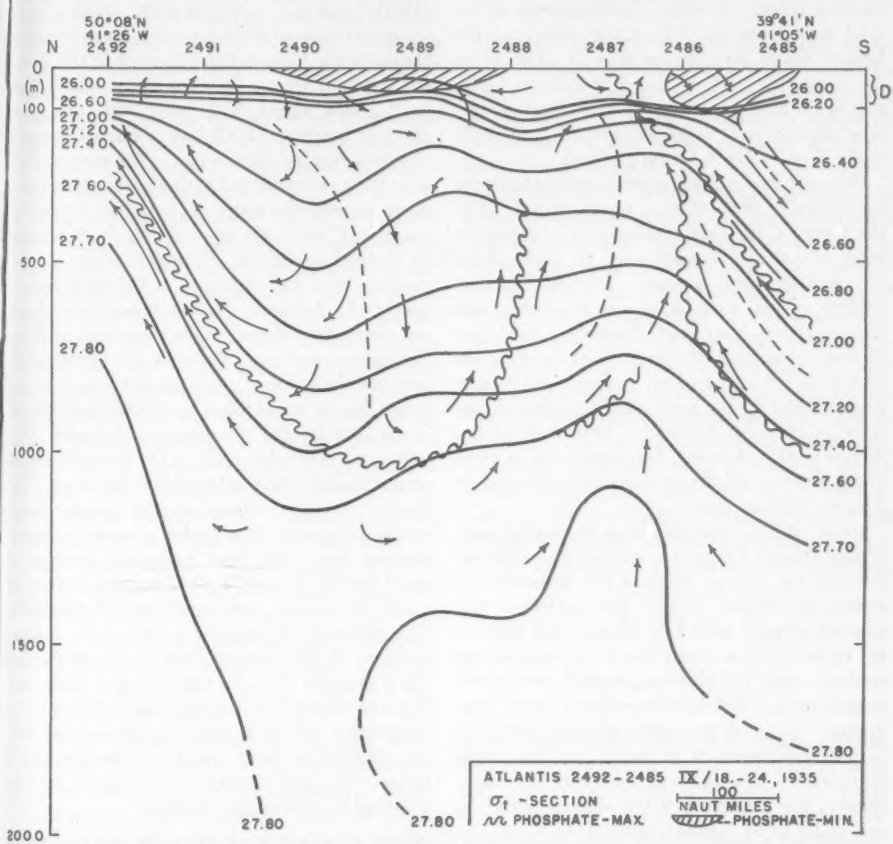

FIGURE 2c. Density section. The arrows indicate the probable lateral and vertical motion as deduced from the phosphate-distribution

velocity in the middle (FIGURE 1a)*. The general theory of Ekman states that the primary effect of the wind is to produce a drift current, whose velocity decreases with depth and which is essentially limited to the upper 50 or 100 m depth. In our model, the total mass transport of water in the layer of frictional influence (D) is directed unequal divergence at different localities, which depends strongly upon details of the wind field, sets up a slope of the sea surface, in our case dropping from south toward the north. For the wind distribution assumed in FIGURE 1a the zone of maximum divergence is to be found at a distance of one-third of the width L of the wind field from the northern border, and the zone of maximum convergence occurs at a distance of one-

* A more detailed study of the problem will be presented in a following paper.

third L from the southern border, as indicated in FIGURE 1c. From this, pressure gradients result in the water, and the consequence are gradient currents in deeper layers, the depth of which depend upon the stratification and the friction of the ocean water.

The condition of steady motion requires that, for each column of water, the divergence of the total mass transport S from the surface to the bottom equals zero, or div $S = 0$. Let S_1 be the mass transport of the drift current layer, and S_2 the mass transport of the gradient current layer, then $S = S_1 + S_2$, and $\text{div}(S_1 + S_2) = 0$, or $\text{div } S_1 = -\text{div } S_2$ for each column.

Only the total mass transport, integrated from the surface to the bottom, is non-divergent. But the layer of frictional influence is a divergent layer, and this divergence must be balanced by divergent gradient currents. Furthermore, this requires vertical motions between the surface and the motionless layer, and therefore a small deflection of the gradient current from the direction of the isobars in the water, or from the direction perpendicular to the total mass transport in the layer of frictional influence. This angle of deflection is still unknown. Information on its value under different conditions would be of interest in dynamic oceanography.

Using selected observations in the central part of the Atlantic Ocean, an attempt was made to estimate the average value of this deflection for regions in the open ocean. The method of calculation is based upon the average wind stress in the vicinity of four closely spaced oceanographical stations, upon the observed density distribution at each station, and the assumption of steady conditions. As far as the results obtained until now permit conclusions, it is found that in middle latitudes, of the northern and southern hemispheres, the magnitude of this angle is about 2°, and in 20° to 30° latitude, about 4° to 5°.

Based upon these values, it seems possible to estimate the total mass transport M of ocean currents due to the wind stress at the sea surface, without knowledge of the density distribution and the depth of the motionless layer. From $\text{div}(S_1 + S_2) = 0$, it follows, in the case of a zonal windfield, that $M = \bar{\tau} L (2\omega \sin \phi)^{-1} \text{cotg } \alpha$ [gr sec^{-1}], where α is the mean value of the angle of deflection for the whole layer, L the width of the wind field, and $\bar{\tau}$ the average stress of the wind. $2\omega \sin \phi$ is the Coriolis parameter. Consider the mass transport of the Gulf Stream through a cross section between 33° N. and 43° N. along 60° W.: Average zonal wind velocity = 7 m sec^{-1}, $\bar{\tau} = 2.1$ dyne cm^{-2}. With $\alpha = 2°$ it follows $M = 74 \cdot 10^6$ m^3 sec^{-1}.

For comparison, let us consider the Antarctic Circum Polar Current between 70° S. and 45° S., using the same wind stress as Munk and Palmén (1951),[13] that is, $\bar{\tau} = 2$ dyne cm^{-2}. With $\alpha = 2°$, the mass transport through a north-south-section of the Antarctic Circum Polar Current in the southern Atlantic Ocean becomes $M = 130 \cdot 10^6$ m^3 sec^{-1}. This agrees fairly well with the value given by Sverdrup (1942),[14] as computed from the observed density distribution. We have to consider these estimates as a preliminary attempt, but if we assume the angle of deflection to be, for example, 1° or 3°, the order of magnitude will not be changed essentially. Therefore, there is some evidence that the dynamics of the Gulf Stream and of the Antarctic Circum Polar Current are not essentially different, when considered as three-dimensional motions. Probably the boundary effects are limited to a much smaller area near the coasts than it would follow by the present theories which consider the two-dimensional model.

We may now refer again to the schematic cross section through the zonal current in FIGURE 1. The gradient current, induced by the average zonal stress, changes the distribution of mass (originally starting from rest with horizontal surfaces of equal density) in such a way, that the surfaces of equal density rise from south toward the north. This inclination is opposite to that of the isobaric surfaces, if the current velocity decreases with depth (FIGURE 1d). In the case of a stationary flow, the vertical velocity distribution $\partial G/\partial z$ of the geostrophic current is related to the vertical density distribution $\partial \rho/\partial z$, and the inclination of the surfaces of equal density (σ_t -surfaces) by the geostrophic equilibrium condition

$$\partial G/\partial z = -(g/l) \text{ tang } \gamma (1/\rho \ \partial \rho/\partial z); \qquad l = 2\omega \sin \phi,$$

where g is the acceleration of gravity, γ the slope angle of the σ_t-surfaces with the horizontal, and z the vertical co-ordinate, positive downwards.

The three-dimensional flow can be considered as a geostrophic current on which lateral and vertical motions are superimposed, so that under stationary conditions the mass transport in the wind drift layer, S_1, toward the south is compensated by a mass transport, S_2, toward the north in the gradient current layer.

Maximum upwelling occurs in the region of maximum surface divergence. This water supply probably will be almost vertical in the nearly homogeneous, wind-stirred, surface layer, but in deeper layers we can assume that this superimposed lateral flow prefers motions along isentropic surfaces. This special type of "austausch" with a dominating average direction may be called "gliding-austausch," similar to the Gleitaustausch in the atmosphere according to Raethjen (1951).[15] In the ocean, the isentropic surfaces are nearly identical with the σ_t-surfaces, and we get a schematic representation of the distribution of lateral flow as indicated in FIGURE 1d. Because of the inclination of the σ_t-surfaces from N to S, we have to assume that the intensity of lateral flow differs essentially in different regions of the cross-section. Below the regions of superficial convergence, the gliding-austausch is bound more to the upper layers and to regions where the slope of the σ_t-surfaces approaches zero. Thus, in these regions, we may assume that the gliding-austausch component along isentropic surfaces is less than in certain deeper layers toward the north, where the ratio "gliding-austausch to vertical motion" is larger. In the southern portion of the cross-section, the vertical component of a sluggish downward motion predominates, whereas in certain other regions, the lateral motion along isentropic surfaces predominates. These features are indicated in FIGURE 1d, comparing region A and B.

There is some evidence in support of the view that the intensity of lateral austausch increases, and the intensity of vertical austausch decreases as the vertical stability increases. This fact has been pointed out already by Parr (1932),[16] and it seems that either the vertical austausch dominates or the lateral austausch. Monotropic lateral austausch tends to smooth the differences in angular momentum, whereas isotropic austausch tends to smooth the differences in the velocity field as well as in other properties of the water masses. According to Raethjen's principle (1951),[15] both types of austausch may be called "antagonists."

This principle can be applied in the same way to the superimposed lateral and vertical flow in the cross-section (FIGURE 1d). The origin of the deep-reaching stationary gradient currents is closely connected with the gliding-austausch in σ_t-surfaces, or, in other words, with the three-dimensional flow. It is evident that without this superimposed flow, and without the water supply by vertical motions, no stationary equilibrium would be possible. Due to the influence of the Coriolis force on the lateral motion along isentropic surfaces, an anticyclonic shear in the current field results, which depends upon the ratio η of monotropic gliding austausch to vertical mixing. Hence

$$\frac{\partial G}{\partial y_s} = \eta 2\omega s \text{ in } \Phi.$$

where y_s means the co-ordinate parallel to the σ_t-surfaces, and positive toward the north. In the case $\eta = 0$, the austausch is completely isotropic, in the case $\eta = 1$, the austausch is completely monotropic, a case which probably will never strictly occur in nature.

The value of η varies from place to place, and in the cross-section (FIGURE 1d) it certainly has a maximum value in the steepest σ_t-surfaces, for example, in region A, where most of the water is shifted toward the zone of maximum divergence at the surface. The effect of this anticyclonic shear in the σ_t-surfaces is to accelerate the current in certain regions toward the divergent zone, and to retard it in regions toward the right hand border, where the dominating isotropic austausch acts to even out the velocity differences. Thus, the austausch-equilibrium tends to force a certain velocity profile upon the wind-driven gradient current. Under stationary conditions, both, the geostrophic equilibrium and the austausch equilibrium must exist. This leads to the equations:

$$\frac{\partial G}{\partial z} = -\sqrt{\frac{g}{\rho}\left(\eta - \frac{1}{l}\frac{\partial G}{\partial y}\right)}\frac{\partial \rho}{\partial z};$$

$$\frac{\partial G}{\partial y} = \eta l - \frac{g}{l\rho}\frac{(\partial \rho/\partial y)^2}{\partial \rho/\partial z},$$

which relate the horizontal and vertical distribution of the geostrophic flow to the field of mass. The value of η turns out to be of the magnitude of 0.1 to 0.5 in the regions of maximum flow of the Gulf Stream. The higher values η are obtained from an analysis of "Atlantis" sections along the east coast of North America, and the lower values from "Altair" sections farther to the east, and some other "Atlantis" sections. A schematic representation of these features is shown in FIGURE 1e. The density and pressure distribution as given by the intermittent stage (FIGURE 1d) becomes gradually adjusted to the new velocity distribution, and the inclination of the σ_t-surfaces steepens in the region to the left of the original main current axis. The end effect is a narrowing of the original current and, under certain conditions, a split-up of

the broad wind-generated current into two branches. Using a more complicated wind distribution, the original current may fork into more than two branches. Whether or not counter currents appear between the narrow swift currents depends highly upon details of the wind field and the final narrowness of the main current branches, that is, upon the value η. This value is closely related to the stratification of the ocean water and the austausch conditions. The condition must be fulfilled that the total mass transport through the cross-section as given by the wind stress, remains unchanged.

FIGURE 2 represents a section through the Gulf Stream obtained by the "Atlantis" along the meridian of about 41° between 39.7° N. and 50.1° N. This section shows the "front-watermass-character" of the flow covering two main current branches in the vicinity of Stat. 2491 and between Stat. 2485–2486, whereas the region between 2486 and 2490 is occupied by a nearly uniform water mass (with the exception of a weak counter current indicated between Stat. 2490 and 2489). This northern portion of the section as far south as Stat. 2488 can be compared with our schematic representation in FIGURE 1e. From the phosphate-distribution in FIGURE 2b a qualitative picture of the probable lateral and vertical flow could be derived, and entered into the density-section FIGURE 2e. Strong lateral gliding-austausch is indicated by the phosphate-distribution between Stat. 2492 and 2491 down to a depth of 1,000 m, whereas in the region of superficial convergence (vicinity of Stat. 2490 and 2489) the phosphate-distribution leads to the conception of a sluggish downward motion with only a very weak gliding-austausch, or no gliding-austausch at all along σ_t-surfaces. The zone of maximum upwelling is located a little north of Stat. 2492, and another zone of maximum upwelling is indicated between Stat. 2486 and 2487. These observations support the ideas shown in FIGURE 1 regarding the distribution of the gliding-austausch.

The flow along the east coast of North America, between Cape Hatteras and the Grand Banks, differs in a certain way from the example considered in FIGURE 1 for a zonal wind field with calm regions at the northern and southern border. The average wind conditions at the East Coast produce mostly a strong maximum divergence just at the continental shelf, and a broader zone of convergence toward the Sargasso Sea. There is some evidence that, under these conditions, the resulting gradient flow tends to form a narrow swift current following immediately the continental slope. In these regions, the high η-values occur, as mentioned above.

Besides other possible effects, which may act in the same direction, it can be stated that the isentropic gliding-austausch probably plays an important part in the formation of the flow pattern of the Gulf Stream, and of other ocean currents, if the vertical stability of the water does not become too weak. If there are regions where the vertical stratification of density is considerable, and currents are present which induce a gliding-austausch strong enough to maintain its place in the "antagonistic fight" of monotropic and isotropic mixing, the gliding-austausch may reinforce the gradient of the velocity field in certain regions along isentropic surfaces. By this, the mass field becomes gradually adjusted to the velocity field, and the density gradient increases, too. Under these conditions, the gliding-austausch can further increase, until a maximum state is attained and a stationary flow occurs, as given by the combined geostrophic and austausch equilibrium condition. Thus, an intensification and a possible split of broad ocean currents into branches may be explained as a mechanism reinforcing itself until it approaches maximum conditions given by the wind stress distribution, and the circumstances which control the austausch motions.

Summary

The paper deals with some characteristic features of the observed flow pattern of the Gulf Stream, that is, the narrowness of main current branches and the possible split of broad wind-generated currents. It is suggested that the three-dimensional flow as a superposition of the non-divergent geostrophic flow, and lateral and vertical motions, be considered. The gliding-austausch along isentropic surfaces in the water probably plays an important part in explaining the observed flow pattern of the Gulf Stream, and of other ocean currents under similar conditions.

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*SECTION OF ANTHROPOLOGY**

"ARCTIC HYSTERIA" AND LATAH IN MONGOLIA†

By DAVID F. ABERLE‡ §

We do not yet understand why certain forms of mental disturbance appear in some cultures and not in others, nor what function is served by the symptoms of various non-Western disorders for the people who manifest them. The data and interpretations offered here can do little but challenge existing theories regarding the first of these questions. They may, perhaps, help to illuminate the second. This paper tries to show that a mental abnormality found in several Mongol groups is identical with Malayan latah,[4-6, 8, 10, 12, 15-17, 20] one form of so-called "arctic hysteria,"[2, 7, 13, 14, 19, 22a] a North African condition,[23] and the "jumping disease" of Maine.[2] The identity of these conditions is used to criticize some theories of the cause of the disease. The paper also attempts to show that latah-like conditions can be differentiated from Gilles de la Tourette's Disease (*maladie des tics*, coordinated, incoordinate, impulsive, convulsive, *etc.* tic).[1, 18, 21, 22, 24, 25] Finally, a tentative explanation of the psychodynamics of the latah-like condition is offered.

The symptom patterns which can be grouped under latah or latah-like behavior* are so similar, from one area and one reporter to another, that they can be characterized in general terms before dealing with the Mongol data. There are two basic groups of symptoms, which may be variously combined.

(1) *The Imitation Reaction.* The most striking feature of latah is the symptom of imitating the actions and words of others (echopraxia and echolalia). Appropriately stimulated, the latah says or does what his tormentor says or does. He may go much further: he may complete a behavior sequence—even one which will injure him—which the instigator merely initiates. He may put his hand in the fire when the instigator merely gestures toward it, or undress completely when some one takes off an outer garment, or jump in the river when some one pretends to start to jump. Or he may carry out a sudden command, even

* A paper by Lewis B. Lockwood, entitled "Industrial Enzymes," was presented at a meeting of the Division of Mycology on April 25, 1952. No abstract of this paper had been received at the time of publication.

† This paper was presented at the meeting of the Section of Anthropology on April 28, 1952.

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§ Based on research for the Mongol Project of the Page School. The Project is supported by the Carnegie Corporation of America and the American Council of Learned Societies. I am indebted to the Dilowa Gegen Hutukhtu, Mr. and Mrs. John Hangin, and Mr. and Mrs. Peter Onon for information on the Mongol mental disease, to Dr. Hyman Lippman for a conversation which was the germ of the interpretation offered here, to Dr. Eduard Ascher for illuminating discussions and for the opportunity to see a case of Gilles de la Tourette's Disease, to Mr. Hans Mijnlieff for bibliographical work and translation from the Dutch, to Professor Evsey Domar and Mr. Henry Michael for bibliographical assistance and translation from the Russian, and to Professor George McT. Kahin, Mr. Owen Lattimore, Dr. Alexander Leighton, Professor Ralph Linton, Dr. Margaret Mead, and Dr. Vilhjalmur Stefansson for discussions, correspondence, and bibliographical leads.

* Throughout most of this paper I shall refer to these behaviors as latah or latah-like, even though this appears to prejudge the case. The term latah is well-established in anthropology, and it seems futile to substitute a Mongol word. I shall take the liberty of using "latah" to refer to the condition or to the person who has it, and the further liberty of referring to Gilles de la Tourette's Disease simply as Tourette's Disease.

when the person who gives it does not provide the latah with any behavioral cues to imitate. The appropriate stimulus may be poking the victim, startling him, or frightening him. It may be enough simply to get his attention.

A severe latah may react imitatively in any novel or disturbing situation, such as meeting a stranger or a superordinate, even when the other person has no wish to provoke imitation. The latah may imitate natural objects or animals, in the absence of any human audience. The latah is powerless to resist the impulse to imitate (there are rare exception[4, 12]) and, according to most authorities, is fully conscious, and aware of the absurdity of his behavior. There is no hypnotic preparation. Tic-like behavior is rare or absent (the importance of this point will emerge later).

(2) *The startle reaction.* The severe latah seems always to show a strong reaction to being startled or frightened. He may jump violently, or freeze, or flee, or turn on the source of his surprise and attempt to destroy it. He may utter a cry and, very commonly, shout obscene exclamations (coprolalia), mostly involving words for male and female genitalia. Objects of fear are variable, but phobic reactions are common: fear of mice, spiders, or snakes, or fear of the words for these animals and alligators, tigers, *etc.* Some people fear the word but not the object.[20] This startle reaction, especially when there is coprolalia, is considered a mild form of latah. Severe latah may first respond to stimulus with the startle reaction and then proceed to imitation, but some seem to show the startle reaction alone, on occasion, and some pass into imitation without first being startled, on occasion.

All reports mention the timidity, passivity, and easy fright of the latah. Frequently severe fright is considered the genesis of latah. For the Jumpers of Maine, the practice of tickling each other in the woods is considered pathogenic.[2] Rarely is the latah psychotic and, if he is, the psychosis is likely to be episodic.* [4, 15] Ordinarily he is a person of normal intelligence who otherwise performs a normal social role. In the arctic, the latah seems to be devalued and derogated (page 325, bibliographic reference 7) but elsewhere this is not characteristic. Latah seems to begin in late adolescence, early maturity, or even later. (But cf. Repond[23]). For every group except the Manchus[22a] and, apparently, the Jumpers, more women than men are afflicted.

Keeping in mind this general picture, derived from Siberian, Manchurian, Malayan, North African, and American materials, let us turn to the Mongol data. The condition is known in Outer Mongolia (*uulgamci* or *orgamci*), in Chahar in Inner Mongolia (*belenci*), in Jehol (*bilenci*), and among the Dagors of Botkha in Manchuria (*belin*). It is known to Kalmuk informants from the Lower Volga (*orgamci*), but no detailed information was received. What follows is based almost entirely on materials provided by three Mongol informants at the Page School.

Here is an example of the full-blown condition. A Khalkha man was known to be very ticklish. People teased him by tickling him. In time, as a result of this (the informant believes) he became latah. The tendency to imitate words or actions was strongly developed and could be provoked by startling or joking with him. Given a lighted cigarette, he could be brought to write with it on the back of his hand, in imitation of a person who pretended to write on his own hand—even though he got burned in the process. If some one pretended to drink water, this man drank until he vomited. Once, slightly drunk, he tried to mount a balky horse, which began to buck. He grabbed the horse's ear, and when people heard the commotion and ran out, they found him holding the ear and jumping frantically along with, and in imitation, of the horse. He could not stop until he was caught and pulled away. He was then deeply grateful for this assistance.

Easily startled, he shouted obscenities, usually the word for male genitals, regardless of the situation. Once, during the consecration of a young Living Buddha, age four or five, the little boy moved from a sitting to a squatting position. The latah correctly assumed that this was a preliminary to urination and began to shout, "Oh, oh, he's going to urinate!" using an obscene epithet for the Living Buddha—one which my interpreter could not translate. Here we find marked imitation of others, and of animals, and the startle reaction and coprolalia occurring in the absence of imitation.

Other Khalkha cases involve: a lama who tipped over a skin bottle full of fermented milk, wanted passionately to right it, but instead had an irresistible impulse to imitate the sound of the milk running out, until it was all gone; a nun who

* Ellis said that he had only one latah in his psychiatric ward, and she was his head nurse, a thoroughly competent and sane individual.[22a]

swayed to and fro for a long time, imitating the swaying of a weed with a tuft of camel's hair caught in it, unable to stop until some one came along and removed the wool. Again, there is imitation of natural objects, without immediate interpersonal stimulation.*

The Chahar informant knew but one latah in a population of 3000. Marked echolalia and echopraxia could be evoked by croaking like a frog, or by getting her attention. She was a middle-aged woman, poor but well-esteemed. The informant's family restrained him from teasing her: it was unkind, they claimed, she might hurt herself, or he himself might become latah from teasing her. The informant does not know if she was coprolalic. Her tormentors were fond of getting her to undress, but some one always stopped her before the process went too far. She recognized her difficulties and begged people not to tease her. She claimed that the condition began when a boy suddenly said, "Look, what a big frog!" She looked, and the frog seemed as big as a sheep. She fainted and was latah thereafter (age at onset is unknown). She had a phobic reaction to frogs.

The Dagor informant tells of a midwife who responded to negative commands. The only way to incite imitation was to do something, or start to do it, and say, "Don't you do it, I will." A boy might squat down in the street and shout "I'm having a baby." Another boy would shout at the midwife, "Don't you deliver it, I will." "No, no," she would say, "I'll do it," and she would rush to minister to the boy. After a moment she would stop and say, "Boys, boys, you shouldn't do that." This trick was played often. She got angry, sometimes reported the boys to their parents, but never struck them. She could be made to run, to bow repeatedly, or to drop objects, by negative command. Once she dropped a child, without serious consequences. (Compare O'Brien.[20]) Without negative command, she would not imitate and did not imitate animals or things. She had a marked startle reaction and would shout, but the informant does not know whether she was coprolalic. She was otherwise healthy, normal, and an esteemed midwife. She said that she became latah after a severe shock: her husband died during the winter. His body was kept in a storage shed because the ground was too hard for a burial. One evening she climbed up in the hut to get some food, fell back on the body, shouted for help, fainted, and thereafter was latah.

There is another group of behaviors which the Mongols separate somewhat from the fully developed syndrome, though in Yukaghir[14] and Malay,[6] at least, they are considered mild forms of latah. These are the phobic and startle reactions, if there is no imitation. Of imitative cases one says, "*ter belenci* (*uulgamci, etc.*)" ["he (she) is latah"]. Of the phobic and startle reactions one says, "*ter belentjine*," "*ter uulgamciljine*," "*ter belindej-aabay*" ["he (she) is acting latah"]. Khalkha, Chahar and Dagor show variability in this matter. There are Khalkha cases of people with mouse phobia who go into a frenzy if they are shown a ball of wool and told that it is a mouse. They lash at it and try to destroy it.* One man feared a particular insect so that if he saw one on his horse he stabbed at it, even though he might wound or kill the horse. He attacked any one who named the insect. Sometimes, even he was teased —if he were unarmed and there were a large crowd present. In Khalkha terminology such phobic cases, and coprolalic cases, are "acting latah." In Chahar, the combination of marked startle reaction and coprolalia is termed "acting latah," but the phobic reaction is otherwise separated from latah. A Chahar woman was easily startled and then shouted the vulgar word for vagina. She did not imitate. Others said, "She is acting latah," but she said, "I am (a) latah." A Dagor man who screamed or uttered obscenities when startled was said to act latah, but another Dagor man with a snake phobia and a fright reaction to the very word snake was said to be "made startled," rather than to be "acting latah." The informant does not know whether the man was coprolalic. The imitative condition is known to one Jehol informant by reputation, but she never saw a case in her own village. The other Jehol informant had not heard of the condition. It should be noted that Jehol is a Sinicized area,[23a] and that latah is apparently unknown to the Monguors, a Sinicized group (Fr. Louis M. J. Schram, personal communication).

Mongol latah is not a common condition (as it is, for example, among the Yukaghir, Yakut,[14] and Malay[6]). The lower age limit for onset is late adolescence, and most cases begin in adults. The

* The first Khalkha case was known to the informant. So-called "nuns" are women who take religious vows late in life, and remain in their own homes. Often they are women of low prestige, *e.g.* poor widows.

* One man who did this would also whip his horse to get it to shy away from a field-mouse in the road. Finally the horse shied automatically. People said jokingly that the horse "acted latah."

imitative condition starts with the phobic or startle reaction and develops from there, but some of those who "act latah" never develop imitation. Women are said to be more susceptible than men. I have little information regarding personality characteristics or social status. Some cases seem to be poor. Of the phobic cases (acting latah), one was a fairly highranking lama and one the brother of a prince. One case of true latah and one of acting latah were midwives, but informants insist that midwives are not especially susceptible. There is no known cure and no desire to cure latah. In fact, people find latah amusing and enjoy having the victims around. The Khalkha informant says that some people pretend latah when they are in a Prince's court, to curry favor, but are in fact not truly latah. He says he has excluded such cases from the data.

Fright is considered an important source of latah. The Dagor informant had no further explanation. The Chahar informant recognizes two types of fright: phobic reaction and severe shock. The woman with a frog phobia exemplifies the former. The informant has no examples of the latter. The Dagor case of the woman who fell on a corpse is perhaps an example of severe shock. The Khalkha informant thinks latah may arise from a severe shock, a crystallized phobic reaction, or imitating some one else for fun. One of his stories tells of a man who became latah through being tickled. He believes that the latah is usually traumatized in adolescence, but his stories do not involve such early events. He tells of a man with a mild mouse phobia whose friends frightened him with a wolf-hide during a rabies epidemic. Thereafter he was strongly latah. Another common source, he says, is a joke in which the phobic object and food are juxtaposed. One man with a mild fear of spiders was fed a dough-cake with a spider in it. When he detected the spider, he became much upset and thereafter was latah. Informants know of no cases among Chinese, Japanese, or Tibetans.

On the basis of rather limited data, I would say that, besides latah, the following mental pathologies are known in various parts of Mongolia: psychotic depressions with suicidal trends, schizophrenic reactions, hysterial paralyses, compulsions, obsessions, phobic reactions, spirit possession, abnormal rages, and mass hysteria. There are no cases of mass latah. Latah is not considered a form of spirit possession.* None of these seems to be common. Abnormal rages fall into three classes: human rabies, delirium, and a psychic condition which sounds a little like Malay amok. The Khalkha informant says that some people brood for several weeks and then go out and kill others. He can give no details, and the pattern sounds less elaborated and less a source of concern than is the case in Malaya.

Comparison of accounts of Malay latah, the imitative form of "arctic hysteria," the North African condition, and the French Canadian (or mixed French-Canadian and American) Jumpers of Maine, with the Mongol *"belenci," etc.*, and "acting *belenci," etc.*, indicates that all of these syndromes are identical, symptom by symptom, except that coprolalia is not mentioned for the Jumpers or for North Africa. The condition is found in Arabs, Negroes, and "mixed" (Arab-Negro?) individuals in North Africa, as well as in one Maltese.[23] Latah is said to exist in Siam,[8] Bengasi,[26] Lapland,[4] the Philippines,[23] and among the Buriat Mongols.[9a] Observers claim to have seen Tamil, Bengali, Sikh, "Nubian,"[20] "Abyssinian,"[12] Eurasian,[8] and "Russian" (non-Siberian?)[7] cases. One writer mentions afflicted Europeans in the Dutch East Indies.[4] I have not seen accounts of the condition from these areas or groups.† In the case of Malay latah, of the Tungus and Manchu behavior, and of the Jumpers, the condition is differentiated terminologically from all other mental conditions, as is true for the Mongols. Authorities on the arctic tend to group latah with other conditions and call them all "arctic hysteria." But Jochelson,[13, 14] Bogoras,[3] and Czaplicka[7] use sub-categories, of which the imitative and startle condition is one, and Jochelson and Bogoras clearly indicate that native vocabulary treats the latah-like condition as a single and separate category. The Russians have a word for it: *meriachen'e* (n.), or *meriachit'* (v.)[9] or *emiriachen'e* (v.)[9a] also transliterated *myriachit, meryachit, etc.* I have found no evidence that the imitative phenomenon is known among the Eskimo.

This distribution, among various climates, cultures, and races, casts considerable doubt on a number of etiological theories. In the first place,

* Professor Linton suggested to me that spirit-possession and latah may be alternative reactions.

† This list, which does not pretend to completeness, is intended to show the less commonly known areas where latah is found. No breakdown into tribes or cultures for the Malayan, Siberian, or Manchurian conditions is given.[7, 15, 22a] It should be noted that I have followed previous writers in including under "Siberian" both Altaic and Paleo-Siberian groups, and under "Malayan" a number of Indonesian groups.

as Czaplikca[7] points out, it is clear that "arctic hysteria" is not a unit phenomenon, but a group of conditions. We may go further: it would seem that "arctic hysteria" is simply a term which covers those forms of mental disease which happen to have been observed in the arctic. If this is true, then the role of arctic climate must be restricted to the frequency of mental disturbances, which seems to be considerable, rather than considered as a cause of the type of disorder. Secondly, Czaplicka suggests that latah may occur when the climate is too hot or too cold, and heat is also mentioned as a causative factor.[6] But the range of climates in which we can now say that latah is found seems to dispose of either hypothesis. Czaplicka also suggests that the disease might be peculiar to the "Mongol" race, but the Maine and the African cases dispose of that. Van Loon[16] says that amok and latah may be companion disorders. This does not seem to be true in the arctic and is dubious for the Mongols, so that not too much weight can be given to the theory. Crude as some of these explanations may seem, they have a recurrent fascination which makes them worth challenging. Unfortunately, the writer cannot offer a substitute theory to explain the distribution of latah. Theories relating to culture areas, social structural features, or to child-rearing practices, which will cover this range of cultures, are hard to conceive of at this point.* Van Loon,[15] Repond,[23] and Linton (personal communication) suggest the possibility of a complex relationship between latah and a submissive social status—a point which cannot be developed here, but which can perhaps be tied in with the conclusions of this paper.

Finally, there is a traditional identification of latah and a peculiar condition best known as Gilles de la Tourette's Disease.[1, 21, 24, 25] This identification is almost surely not justified. Tourette's disease is characterized by: (1) fairly elaborate tics, often including not only the face, but the trunk and extremities as well; (2) explosive utterance of obscure noises or of obscene words (coprolalia); (3) echolalia; (4) echopraxia; and (5) jumping. Except for the tic, all these phenomena are common in latah, but there are major differences between the two conditions. I have examined accounts of 18 cases of Tourette's Disease,[1, 13, 21, 22, 25] and have seen and talked with one case. The only features common to all 19 are: tic and explosive utterances of noises or obscenities. In latah, on the other hand, there is almost nothing resembling tic. Occasional comments which might indicate otherwise[4, 6, 7] seem to concern imitations of others' expressions or manneristic behavior. Mongol informants know of cases of tic and choreiform movements and consider them entirely distinct from latah. Furthermore, coprolalia in the two conditions takes different forms. In Tourette's Disease, corprolalia is "spontaneous," occurring in the absence of specific stimulation. Indeed, a situation of silence or polite conversation often provokes the irresistible impulse to burst out. The utterances are explosive, forced out against heroic efforts to contain them, which gives them a unique vocal quality. Latah coprolalia occurs only when the person is startled or otherwise stimulated, never spontaneously, and the vocal effect is that of a normal shout or exclamation. The echolalia and echopraxia of Tourette's Disease are often "delayed," that is, the person incorporates into his stereotyped behavior words or actions he has observed or heard, hours or even days after the event.* Latah imitation occurs on the spot, or not at all, and the "jumping" of Tourette's Disease seems to be only a manifestation of major tic, in at least 50 per cent of cases.† In latah, the jump is a straight reaction to shock or surprise.

Tic and obscure, or obscene, forced utterances, then, are the pathognomic features of Tourette's Disease. Echolalia, echopraxia, and marked startle reaction are frequent or occasional accompaniments. Either imitation, or startle reaction with coprolalia, or both, are the pathognomic features of latah. We would not expect to find tic. A man with Tourette's Disease is committed to a life of automatic behaviors which are provoked by endogenous stimuli—by a mounting feeling of pressure which culminates in tic and explosive utterances. He makes the observer distinctly uncomfortable and is often barred from ordinary social and economic life. The latah responds in his way to a variety of exogenous stimuli, and is condemned to a life of teasing by people who find him amusing but not objectionable.‡ Finally, Tourette's Dis-

* Mr. Lattimore suggested to me that latah seems to be found where the community constitutes a face-to-face, slightly isolated group.

* Echolalia present in 13 cases, echopraxia, the most striking feature of latah, in but four. In three cases of echolalia and one of echopraxia, the behavior is "delayed." Careful observation might reveal that this is the case in even more cases, but true echolalia and echopraxia do occur.

† Jumping is mentioned only by de la Tourette. It occurs in six out of nine cases, but in three it is an elaborate motor tic; in two it is a startle reaction; and in one case evidence is lacking.[25]

‡ The negative reaction to Tourette's Disease is almost surely not cultural. Two Mongols who observed a case of Tourette's Disease at the Hopkins Hospital found his behavior disturbing and not at all amusing. They considered him pitiable.

ease is more common in men than in women and frequently begins in childhood.

Until recently, no observers ever saw both conditions. De la Tourette and others depended on written accounts and on symptom-labels, rather than detailed behavior patterns, to establish the supposed identity. Van Brero,[4] who saw many cases of latah, thought it unlike Tourette's Disease, for reasons similar to those given here. At Hopkins, it was possible to show a case of Tourette's Disease to two Mongols and to one Hollander who grew up in the Netherlands East Indies, all of whom knew latah. So far as is known, this is the first time that any observers have seen both conditions. All three stated that the case they saw was unlike latah: because of the tic, because of the continued, unprovoked obscene shouts, and because (in this case) there was no immediate imitative behavior. This evidence, and the contrasts mentioned above, seem to militate against the identity of the two syndromes, even though they may conceivably belong to the same "family" of diseases.

Let us now consider the problem of interpreting the psychodynamics of latah. It would seem plausible to understand the imitative behavior as a defense, and more specifically as a very simple form of "identification with the aggressor."* Anna Freud says that this mechanism may be used for defense against either external dangers or instinctual stimuli, and that it involves assimilating oneself to, or identifying oneself with, the dreaded source of danger.[11] One example sounds a little like latah. A teacher noted that when he scolded one of his pupils, the boy made faces which amused the entire class. The teacher thought that the boy was mocking him, or perhaps that he had a tic. It developed that the boy's faces caricatured the teacher's expressions during the scolding: that when the boy had to face the scolding "he tried to master his anxiety by involuntarily imitating" the teacher (see p. 118 of Reference 11). If we examine latah behavior with this in mind, we may find ourselves closer to a solution. It would appear that the latah is defending himself in various ways against the fear of being overwhelmed. The defense takes four forms: imitation (identification with the aggressor), destruction of the stimulus, flight (not exemplified here), and coprolalia. Discussion of this last defense will be deferred. The onset of latah suggests its defensive character. Some victims suffered a shock, some women date the onset from traumatic sexual dreams of being attacked by men or by male genitalia,[4, 15–17] and some were unable to tolerate being tickled. In this last event, it must be noted on the one hand that being tickled is a somewhat erotic experience, and on the other that it renders the victim helpless and usually results in his begging for release. The traumatic dreams are a similar fusion of the erotic and of something overwhelming, *i.e.*, an attack. The phobic reactions, and the Mongol data in general, are more refractory to direct interpretation, but without stretching the point we can be quite confident that the phobia, like the dream, indicates not just a fear of the external object, but the presence of an internal danger, arising from disturbing unconscious material. It is in this connection that we should consider the defense of coprolalia. Apparently, the latah faces a double danger: a threatening outside world, and unconscious material which is evoked by certain stimuli in that outside world. In coprolalia there may be a compromise technique: the shout seems to drive back the unconscious material, and on the other hand the material is allowed a partial, but involuntary and "meaningless" expression in the very choice of words.* This interpretation closely resembles Ascher's views on coprolalia in Tourette's Disease.[1] At this one point it is possible that the two syndromes meet as branches of the same general condition. To reformulate, latah cases seem to fear being overwhelmed by the outside world, or being surprised into betraying some forbidden but urgent inner need Their bizarre behavior is a defense against a chaotic reaction. They "go over to" (identify with) the stimulus, flee from it, destroy it—or stifle the unconscious material with a cry.†

Why this defense, so uniform in symptoms, is found in so many areas and is apparently absent in so many others; why one person, rather than another, falls prey to latah; why the condition is common among Yukaghir, Yakut, and Malay and rare in Mongolia; and what social roles claim most of the victims, are questions which still clamor for answer. Perhaps later research will

* I am indebted to Dr. Hyman Lippman for this suggestion.

* It must be noted, however, that among the Mongols the exclamation may be, "God!" or other non-obscene words and phrases.

† This interpretation is not phrased in terms of specific interpersonal or role contexts. Such a formulation might be desirable, but it should be remembered that latah behavior can occur in the absence of human stimulation, as seen in the imitation of animals and objects. Shirokogoroff attempts an explanation in terms of social role and social situation.[22]

shed light on these problems.* My present guess (and it is only that) is that the latah's problem is one of disturbance and ambivalence with respect to submissive behavior, that this disturbance is based on an unconscious connection between submission and a dreaded and desired passive sexual experience akin to being attacked,† and on the idea that the world stands ready to "overwhelm" the victim in this double sense.

This approach to latah as a defense mechanism seems to offer promise for a more encompassing interpretation which will give due attention to social and cultural factors. For example, this analysis can be related to the observation that in many areas most of the cases are women, and to the apparent fact that latah occurs more commonly among individuals in a subservient or submerged social position, and is particularly easy to evoke when the instigator is a person of authority or prestige. But what has been said here must be considered speculative and subject to correction—presented, as it is, in the hope that it may be of some assistance in further explorations of the problem.

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* If there are still "Jumpers" in Maine, or, as Beard believed, in Michigan,[2] personality studies could be carried out. The Russian materials (cf.[9, 9a]) merit further exploration.

† Cf. van Loon.[15] In utilizing psychoanalytic concepts, I make no assumptions regarding the universality of specific defense mechanisms or of specific unconscious material. Shirokogoroff considers that the function of latah may vary from group to group, and that the unconscious complex expressed in the startled cry may also vary.[22a]

CONFERENCES HELD

SECTION OF BIOLOGY

"ORAL FAT EMULSIONS AND THEIR USE IN MEDICINE"

APRIL 29, 1952

The Section of Biology held a Conference on "Oral Fat Emulsions and Their Use in Medicine." Doctor Frederick J. Stare, Harvard School of Public Health, Boston, Massachusetts, was the Conference Chairman in charge of the meeting.

The program consisted of the following papers:

Tuesday, April 29

Morning Session

"Introductory Remarks," Frederick J. Stare, Harvard School of Public Health, Boston, Mass.

"The Importance of Fat in the Diet," R. W. Swift, Pennsylvania State College, State College, Pa.

"Fat Absorption and the Experimental Basis of Oral Fat Emulsions," Robert P. Geyer, Harvard School of Public Health, Boston, Mass.

"Clinical Studies on the Use of an Oral Fat Emulsion," Milton Shoskhes, Bronx Veterans' Hospital, Bronx, N. Y.

"Metabolic Studies with Oral Fat Emulsions," T. B. Van Itallie, Harvard School of Public Health, Boston, Mass.

"Oral Fat Emulsions in the Feeding of Patients with Severe Burns," S. M. Levenson, Army Medical Nutrition Laboratory, Chicago, Ill. and Medical College of Virginia, Richmond, Va.

Afternoon Session

"Fat Ingestion and Chylomicrons," H. Necheles, Michael Reese Hospital, Chicago, Ill.

"The Use of Oral Fat in Hyperalimentation and Parenteral Alimentation," Anthony A. Albanese, St. Luke's Convalescent Hospital, Greenwich, Conn.

"The Use of Oral Fat Emulsions in Experimental and Clinical Medicine," Arthur Grollman, Southwestern Medical School of the University of Texas, Dallas, Texas.

"The Use of Oral Fat in Surgical Patients," Irving F. Stein, Jr., Edward Goldberg, and Karl A. Meyer, Northwestern University Medical School, Chicago, Ill.

"The Use of Oral Fat Emulsions in Supportive Treatment of Tuberculosis," Morris E. Dailey, University of California School of Medicine, San Francisco, Calif.

"Clinical and Physiologic Studies with the Use of Oral Fat Emulsions in Patients," W. R. Waddell, Massachusetts General Hospital and Harvard School of Public Health, Boston, Mass.

"Absorption of Emulsified Lipid Orally in Pancreatic Insufficiency in Infants and Children," Charles D. May and Charles U. Lowe, College of Medical Sciences, University of Minnesota, Minneapolis, Minn. and University of Buffalo Medical School, Buffalo, N. Y.

"Oral Fat Emulsions Combined with Protein Supplements as Supportive Therapy in Acute Poliomyelitis," George J. Boines, Wilmington, Del.

"Laboratory and Clinical Studies Following the Use of Oral Fat Emulsions," S. D. Jacobson, Wayne County General Hospital, Eloise, Mich.

"Forced High Calorie Diets in the Treatment of Uremia," W. J. Kolff, Research Division, Cleveland Clinic, Cleveland, Ohio.

Evening Session

"Importance of Calories in Growth of Children," I. M. Hoobler, Children's Fund, Detroit, Mich.

"Interrelation of Food Stuffs," J. P. Peters, Yale University, New Haven, Conn.

The Section of Biology provides conferences for active workers in the special fields of Biology.

Attendance is limited to those invited to participate in these conferences and to interested Members of the Academy.

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Elected April 24, 1952

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